# Predicting the risk of post-discharge medication related harm in older adults

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# Predicting the risk of post-discharge medication related harm in older adults

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# Abstract

Older people are at an increased risk of experiencing medication related harm (MRH), but it is not clear which older people are at greatest risk. Multivariable risk prediction models target interventions at patients stratified by their risk of developing a specific outcome over time. An MRH risk prediction model could prioritise care for high-risk older patients at the point of discharge - a time of heightened patient vulnerability. The overall aim of this thesis was to examine the possibility of identifying older patients at risk of MRH following discharge from hospital.

To achieve this, three distinct studies were conducted; Study 1 was a systematic review of MRH risk prediction models which informed the development of a conceptual framework and the design of Study 2. Study 2 involved conducting a prospective cohort study to determine the incidence, and describe the characteristics, of MRH in an older population discharged from a United Kingdom (UK) teaching hospital. Patients discharged from acute care were recruited and followed up for 8 weeks. A review of any re-admission, General Practice (GP) notes, and a patient telephone interview were used to determine if MRH had occurred. Likelihood, preventability, severity and the medicine(s) involved were determined. MRH was defined as harm from medicines due to an adverse drug reaction or failure to receive a medicine (including non-adherence). Study 3 identified variables associated with MRH focussing on physiological and psychosocial domains.

Following an extensive literature search of over 13,000 articles, Study 1 identified only five risk prediction models of modest quality, all focussing on adverse drug reactions (ADRs), mainly drawing on physiological variables to predict medication harm and none related to the post-discharge period. Four had undertaken some validation but displayed only modest performance (Area Under Receiver Operator Curve (AUROC) 0.62-0.73), rendering them unsuitable for routine clinical use. This systematic review and a review of the wider literature around MRH led to the design of a conceptual framework, drawing together physiological and psychosocial variables and highlighting commonalities between MRH and frailty to build a theoretical model of the factors involved in medication harm.

The prospective cohort study recruited 396 patients during their in-patient stay in the older persons' unit, (mean age 83±7 years, Charlson comorbidity index (CCI) 2.16±1.63, mean Barthel index 13.24±4.56, 55% received a package of care) and highlighted that two in five frail patients experienced MRH, 88% of which required treatment modification and more than half were preventable. Approximately a third required re-admission. Non-adherence contributed to approximately one third of the MRH incidents. Medicines acting on the central nervous system were responsible for the majority of MRH (25%).

Physiological and psychosocial variables were associated with MRH at a univariate level: number of medicines (odds ratio (OR) 1.10 [95% confidence interval (CI) 1.05-1.16, p<0.0001]), antithrombotics (OR 1.71 [95%CI 1.12-2.60, p0.01]), antihypertensives (OR 1.55 [95%CI 1.03-2.33, p0.04]), MUST score (OR 1.92 [95%CI 1.12-3.29, p0.02]), and hand grip strength (men) (OR 0.93 [95%CI 0.89-0.98]).

A higher than expected re-admission rate was reported; 156 patients (39%) were re-admitted, 67 with MRH. Sub-analysis revealed a mean time to event of 48.9 days (95% CI 47.3-50.6) and when compared to those not re-admitted, identified additional variables associated with MRH: use of a multi-compartment compliance aid (MCA) (chi square 9.76, p 0.002), CCI (hazard ratio (HR) 1.14 [95% CI 1.01-1.29, p0.03]) and depression (HR 1.04 [95% CI 1.01-1.08, p0.02]). Number of medicines was also significant (HR 1.10 [95% CI 1.05-1.15, p<0.01]) and was the only variable to retain significance upon multivariate analysis. There was little difference between patients re-admitted with MRH and patients re-admitted without MRH with only number of medicines reaching statistical significance (OR 1.08 [95% CI 1.01-1.17, p0.04]). All re-admitted patients were frail.

The heterogeneity of an older population, due to advancing age and frailty, makes the identification of a small number of highly predictive variables challenging and may limit the usefulness of pursing the traditional path of risk prediction modelling. The study population were frail and given the high prevalence of low reserve, the significance of the number of medicines may represent both a greater illness burden, and increased likelihood of exposure to potential medicine related insult thus an increased risk of MRH. This study suggests that MRH is similar to geriatric syndromes; it is multifactorial, occurs when there is an accumulation of deficits across multiple systems, and renders the patient vulnerable to situational challenges. In light of this,

energies may be better expended exploring the clinical utility of a frailty index to stratify the risk of MRH in this complex population.

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confidence to stretch ourselves, to question the status quo, and support us as we looked to the horizon. In particular, to my selfless mum to whom I would like to dedicate this thesis. She taught me the joy that caring for others can bring, especially older adults, and the value of the older generation to our society.

# Abbreviations

| Abbreviation | Meaning |
|---|---|
| ADR | Adverse Drug Reaction |
| A&E | Accident and Emergency |
| ACE | Angiotensin Converting Enzyme |
| ADE | Adverse Drug Event |
| ADL | Activities of Daily Living |
| AF | Atrial Fibrillation |
| AKI | Acute Kidney Injury |
| ALT | Alanine Aminotransferase |
| AMTS | Abbreviated Mental Test Score |
| ARB | Angiotensin Receptor Blocker |
| AUROC | Area Under Receiver Operator Curve |
| BADRI | Brighton Adverse Drug Reaction Risk |
| BAPEN | British Association for Enteral and Parenteral Nutrition |
| BMI | Body Mass Index |
| BNI | British Nursing Index |
| BPH | Benign Prostate Hypertrophy |
| CCF | Congestive Cardiac Failure |
| CCGs | Clinical Commissioning Groups |
| CCI | Charlson Comorbidity Index |
| CHD | Coronary Heart Disease |
| CI | Confidence Interval |
| CINAHL | Cumulative Index to Nursing and Allied Health Literature |
| CIRS | Cumulative Index Rating Scale |
| CIRS-G | Cumulative Index Rating Scale-Geriatrics |
| CIT | Cognitive Impairment Test |
| CKD | Chronic Kidney Disease |
| CNS | Central Nervous System |
| COAD | Chronic Obstructive Airways Disease |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| CV | Cardiovascular |
| CVD | Cardiovascular Disease |
| CVS | Cardiovascular System |
| DRP | Drug Related Problem |
| EDL | Electronic Discharge Letter |
| eFI | Electronic Frailty Index |
| eGFR | Estimated Glomerular Filtration Rate |
| EPC | End Point Committee |
| EPV | Events Per Variable |
| ETOH | Alcohol |
| EWGSOP | European Working Group on Sarcopenia in Older People |
| F | Female |
| FI | Frailty Index |
| GAD | General Anxiety Disorder |
| GI | Gastrointestinal |
| GIFA | Gruppo Italiano di Farmacoepidemiologis nell Anziano |
| GP | General Practice/General Practitioner |
| GSTFT | Guy's and St. Thomas' NHS Foundation Trust |
| GTN | Glyceryl Trinitrate Spray |

| Abbreviation | Meaning |
|---|---|
| GU | Genitourinary |
| Hb | Haemoglobin |
| HES | Hospital Episodes Statistics |
| HMR | Home Medication Review |
| HR | Hazard Ratio |
| HTN | Hypertension |
| IADL | Instrumental Activities of Daily Living |
| ICU | Intensive Care Unit |
| ICD | International Classification of Disease |
| IHD | Ischaemic Heart Disease |
| IPA | International Pharmaceutical Abstracts |
| IPE | Inter-professional Education |
| IQR | Inter-Quartile Range |
| ISMN | Isosorbide Mononitrate |
| KCL | Kings' College London |
| LDL | Low Density Lipoprotein |
| LTC | Long Term Condition |
| MAI | Medicines Appropriateness Index |
| MARS | Morisky Adherence Rating Score |
| MCA | Multi-compartment Compliance Aid |
| MI | Myocardial Infarction |
| MMSE | Mini Mental State Examination |
| MNA | Mini-Nutritional Assessment |
| MR | Medicines Reconciliation |
| MRH | Medication Related Harm |
| MSK | Musculoskeletal |
| MSU | Midstream Urine |
| MUR | Medicines Use Review |
| MUST | Malnutrition Universal Screening Tool |
| NeLM | National Electronic Library for Medicines |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute of Health Research |
| NNT | Numbers Needed to Treat |
| NR | Not Reported |
| NRS | Nutritional Risk Screening |
| NSAIDS | Non-Steroidal Anti-Inflammatory Drugs |
| OPU | Older Persons' Unit |
| OR | Odds Ratio |
| OTC | Over-The-Counter |
| PADR | Preventable Adverse Drug Reaction |
| PADR-EC | Predicting Adverse Drug Reactions in Elderly Community Dwelling |
| PHQ | Patient Health Questionnaire |
| PIMS | Potentially Inappropriate |
| PIP | Potentially Inappropriate Prescribing |
| POC | Package of Care |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-analyses |
| PRN | When Required |
| PROGRESS | Prognosis Research Strategy |

| Abbreviation | Meaning |
|---|---|
| PUD | Peptic Ulcer Disease |
| PVD | Peripheral Vascular Disease |
| REC | Research Ethics Committee |
| RfPB | Research for Patient Benefit |
| SD | Standard Deviation |
| SGA | Subjective Global Assessment |
| SOB | Shortness of Breath |
| START | Screening Tool to Alert Doctors to Right Treatment |
| STOPP | Screening Tool of Older Persons' Potentially inappropriate Prescriptions |
| TRIPOD | Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis |
| UK | United Kingdom |
| UPIN | Unique Patient Identifier Number |
| US | United States |
| USA | United States of America |
| UTI | Urinary Tract Infection |
| WBC | White Blood Cell |
| WHO | World Health Organisation |
| WHO-ATC | World Health Organisation Anatomical Therapeutic Classification |
| #NOF | Fractured Neck of Femur |

# Publications

Peer reviewed journal articles and abstracts, and presentations relating to this thesis

**Journal Articles:**

**Stevenson JM**, Parekh N, Ali K, Timeyin J, Bremner S, van der Cammen TJ, Allen J, Schiff R, Harchowal J, Davies JG, Rajkumar C. Protocol for a Prospective (P) study to develop a model to stratify the risk (RI) of medication (M) related harm in hospitalized elderly (E) patients in the UK (The PRIME study). BMC Geriatr. 2016;16:22.

Gudmundsson A, **Stevenson JM**, Petrovic M, Somers A, Onder G, Callens S, van der Cammen TJ. Challenges and risks for older travellers with multimorbidity: Focus on pharmacotherapy. Eur Geriatr Med. 2016 Sep;7(5):407-10.

Tangiisuran B, Scutt G, **Stevenson JM,** Wright J, Onder G, Petrovic M, van der Cammen TJ, Rajkumar C, Davies JG. Development and Validation of a Risk Model for Predicting Adverse Drug Reactions in Older People during Hospital Stay: Brighton Adverse Drug Reactions Risk (BADRI) Model. PLOS ONE 2014 Oct 30;9(10):e111254.

**Stevenson JM**, Williams JL, Burnham TG, Prevost AT, Schiff R, Erskine SD, Davies JG. Predicting adverse drug reactions in older adults; a systematic review of the risk prediction models. Clin Interv Aging. 2014 Sep; 1581.

**Abstracts:**

**Stevenson JM**, Kindsiko K, Ikpemo C, Williams JL, Schiff R, Davies JG. Assessing ADR risk in older patients: do the prediction models agree? Age Ageing. 2013:42(suppl 3):iii26 doi:10.1093/ageing/aft107. Abstract. *(Prize nominated)*

**Stevenson JM**, Erskine SD, Williams J, Burnham T, Schiff R, Davies JG. Predicting medication related risk in the elderly; a review of validated tools. Eur Geriatr Med. 2012;3:S129. Abstract.

**Presentations:**

**Stevenson JM**. Dosette box dilemma. **Kent, Surrey and Sussex Academic Health Sciences Network Polypharmacy in Older Adults event.** Brighton. April 2017

**Stevenson JM**. Predicting medication related harm in older adults: a review of the validated models. **NIHR CLAHRC Northwest London Medicines optimisation and patient safety learning event.** London. January 2017

**Stevenson JM**. Medication related return journeys. **British Geriatrics Society autumn meeting.** Brighton. October 2015.

**Stevenson JM**. Medication across borders. **European Geriatrics Society (EUGMS) Congress**. Rotterdam. September 2014.

**Stevenson JM**. Predicting medication related problems in older people. **King's Health Partner Clinical Development Group: Risk Prediction in Translational Medicine**. King's College London. March 2013.

**Stevenson JM**, Kindsiko K, Ikpemo C, Williams JL, Schiff R, Davies JG. Assessing ADR risk in older patients: do the prediction models agree? **Institute of Pharmaceutical Science Annual Research Symposium.** King's College London. May 2013.

**Stevenson JM**. Predicting medication related problems in older people. **Older People Pharmacy Network annual study day.** East & South-East England Specialist Pharmacy Services, Medicines Use and Safety Network, London. November 2012.

**Stevenson JM**. Use of medicines at the extremes of age: Predicting medication related problems in older people. **King's Health Partners Pharmaceutical Science Clinical Academic Group Inaugural Symposium.** King's College London. September 2012.

## Declaration

I, Jennifer M. Stevenson, declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

# Chapter 1 Introduction

"Res eadem vulnus opemque feret".[1] The same medicine will both harm and cure me. This paradoxical outcome of taking medicines has long been recognised, and while the severity of such harm may vary, it is responsible for a significant proportion of hospital admissions in older adults.[2] In a globally ageing population, as the prevalence of multimorbidity increases and the number of prescribed medicines grows it is essential that we investigate this risk, with the aim of identifying patients most likely to suffer harm from their medicines. Cases can then be prioritised, and interventions targeted to reduce the burden of medication related harm (MRH) for both patients and the healthcare system.

## 1.1 Definitions and terminology

When conducting research in the area of MRH it is necessary to consider the different definitions and terminology used. Described as a Tower of Babel of terminology[3], a multitude of terms have emerged, many with overlapping yet conflicting jurisdictions. It is therefore important to understand the meaning of these terms to allow accurate comparison of the literature.

### 1.1.1 Drug related problems

Drug (or medication) related problem (DRP) is perhaps the broadest of terms and is often used interchangeably with adverse drug events (ADEs). Defined by one group as "a circumstance related to the patient's use of a drug that actually or potentially prevents the patient from gaining the intended benefit of the drug", there are at least 14 different classification systems.[4] These systems focus on: drug choice problems (errors, substitutions, discontinuations/omissions, use of unnecessary drugs); dosing problems (dose changes, cancellations, omissions); drug use problems (lack of knowledge, lack of understanding, non-adherence); interactions and adverse drug reactions.[5] For example, the Swedish-developed Westerlund System[4], which accommodates over-the-counter (OTC) and herbal medicines, consists of the following 13 categories: 1. uncertainty about the aim of the drug; 2. drug duplication; 3. interaction; 4. contraindication; 5. therapy failure; 6. adverse reaction; 7. underuse of drug; 8. overuse of drug;

9. inappropriate time for drug intake/wrong dosage interval; 10. problem administering drug; 11. difficulty opening container; 12. inappropriate storage of drug and 13. other.

### 1.1.2 Adverse drug events

ADEs are commonly defined as "an injury resulting from medical intervention relating to the drug"[6]. This includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuation of drug therapy). This term is often applied in the literature when reductions or discontinuations are deemed inappropriate, and so ADE has become closely associated with medication errors.[7]

### 1.1.3 Adverse drug reactions

Frequently, and incorrectly, ADE and ADR are used synonymously. ADR, as defined by the World Health Organisation (WHO) refers to "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for modification of physiological functions".[8] This was later refined by Edward and Aronson to improve its utility in clinical practice through the inclusion of medication error. They defined an ADR as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product"[9]. According to this definition all ADRs are considered to be ADEs and some of these will be due to a medication error.

### 1.1.4 Medication error

Medication errors are described as "preventable events that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer".[7] They can occur during any stage of the medication journey including compounding, prescribing, dispensing or administration. Medication errors do not harm the patient but a small proportion may result in harm.

Nebeker and colleagues[7] provide a useful diagrammatic summary of the terminology used to describe different types of harm from medicines, and the relationship between them (see Figure 1.1).

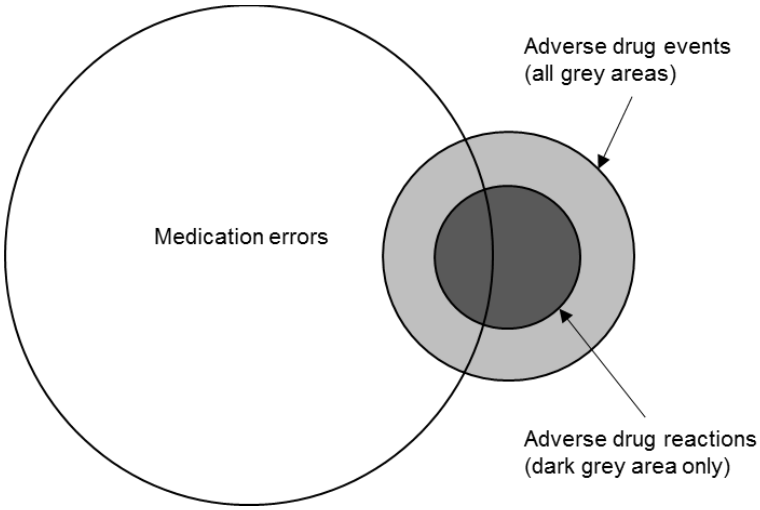



Figure 1.1 Relationship between the types of harm from medicines (adapted from Nebeker et al.[7])

### 1.1.5 Medication related harm

This thesis defines and uses the term medication related harm (MRH) as an umbrella term when referring to harm from medicines in general and as the specific outcome measure used in the prospective cohort study described in Chapter 4. Agreed by an international, multidisciplinary expert panel, MRH incorporates ADRs and failure to receive medicines (including due to failure in the supply chain and non-adherence). This term was derived to more accurately reflect the challenges presented to older adults when prescribed medicines, and was measurable given the resources available. Its derivation is described in more detail in Chapter 4. Importantly, it does not relate to medication errors which account for a very small proportion of harm[10] and has its own body of literature.

## 1.2 The size of the problem

There is great variation in the reported incidence and prevalence of MRH, much of which may be attributed to the outcome measured (usually either an adverse drug event (ADE) or an adverse drug reaction (ADR)), the setting (inpatient or community) and the population studied (often all ages or over the age of 65 years).

### 1.2.1 Inpatients

In a recent review of observational studies from across Europe, 16 papers reporting the rate of adult inpatient ADR (including ADEs and DRPs) were identified.[11] Three focussed specifically on older adults. A median ADR rate of 11.9% (range1.7-81.3%) was reported for the 13 studies that were not restricted by age. The study with the highest incidence was conducted in Norway across 5 different centres over a 6-month period and recruited 827 patients from internal medicine and rheumatology departments who were assessed for DRPs through intensive chart review. The high incidence reported is likely to reflect the broad outcome measure of DRP which included "need for laboratory test" and "therapy discussions". DRPs related to ADRs were experienced in 7.8% of patients which may be a more valuable comparator and is consistent with several other European studies which measured ADRs specifically.[12–14] All three studies focussing on older adults measured ADR as defined by the WHO[8], the incidence of which ranged from 11.5-60.7%.[15–17] Two further studies in patients over the age of 65 years, which weren't included in the review as the data were collected or the paper was published outwith the defined time period, reported ADR rates of 6.5%[18] and 12.5%[19]. This large variation in incidence in studies using the same outcome measure is possibly due to different methods of identification of ADR and differences in the populations studied.

### 1.2.2 Community

Few studies have explored the prevalence of MRH occurring in the community. Only two, in patients over the age of 18 years, were identified in a review of the European literature which focused on studies published since January 2000.[11] Investigating ADEs in Swedish adults, these were two large population-based studies, conducted by the same research group in Sweden. ADEs were identified via self-reporting in one study and through review of patient medical records in the other. The reported ADE rate was 19.4% (95% CI 18.5-20.3%) and 12.0% (95% CI 11.1-12.9%) respectively.[20,21] The lower prevalence reported via medical record review is consistent with previous studies.[22] The population differences may explain some of this variance, for example, the self-reporting population were older, mean age 53.2±18.2 years compared to 48.9±19.0 years for the medical records review population, however the outcome data source will have also influenced the prevalence.

#### 1.2.2.1 Post-discharge

A sub-set of the community-based literature are those studies which investigate post-discharge MRH. Representing a discrete population, these studies explore MRH in patients during a time of heightened vulnerability following admission to hospital.[23]

A review of articles reporting DRPs in patients over the age of 60 years old discharged from hospital and interventions to reduce them, published between January 1998 and December 2009, identified 23 papers meeting the inclusion criteria. Fourteen were cross-sectional or cohort studies reporting the prevalence and incidence of DRPs, and nine were quasi-experimental or clinical trials reporting the outcomes of an intervention. The majority were conducted in the United States (US); one was conducted in the United Kingdom, however only data relating to the intervention was reported. The review authors concluded that differences in study design, outcome measures and patient populations limits comparisons and results in a wide-ranging prevalence (14-46%).[24] The quality of the studies was also questioned with over half (56.5%) subject to selection bias due to a small sample size (the number of participants ranged from 68-808). The highest quality studies were clinical trials and cohort studies, which met 82% and 70% of the quality criteria respectively. The clinical trials focussed on post-discharge interventions and did not report the incidence of DRPs, and only two of the cohort studies reported the incidence of DRPs and are summarised in Table 1.1[25,26]. The other two cohort studies reported the incidence of non-adherence (30.6% of patients were under-adherent and 18.4% were over-adherent during the two weeks following discharge)[27], and the incidence of medicine modifications in the month after discharge (37.5±25.4%)[28]. Additional studies regarding post-discharge MRH that were not included in the review, because they did not meet the inclusion criteria or were published after the review period, are also described in Table 1.1.

Table 1.1 Summary of frequency and types of DRPs in older adults after discharge from hospital

| **Study (country)** | **Setting (duration)** | **Method** | **Patient age (sample size)** | **Post-discharge review period** | **Method of assessment of causality** | **Primary outcome** | **Incidence** |
|---|---|---|---|---|---|---|---|
| Ellitt, 2010[29] (Australia) | GP practices (36 months) | Retrospective cohort. Patients discharged home from Cardiology unit with at least one cardiac drug and had a HMR on GP system. HMR reviewed for DRP | Not specified Mean age: 66±13.2 years (n=76) | NR | Blinded research pharmacist. No standardised assessment used | DRP (Westerlund System) | 93.3% (Patient uncertainty about indication 32%; potential interaction 22.4%; ADR 15.1%) |
| Hanlon, 2006[26] (USA) | Veteran Affairs Medical Centres (3.5 years) | Prospective cohort. Patients discharged from medical or surgical wards following 48-hour minimum stay with at least 2 of 10 frailty criteria | > 65 years Mean age: NR 46.4% >75 years (n=808) | 1 year | Blinded geriatrician and geropharmacist pairs using Naranjo algorithm | ADR | 33% (1.92 events per 1000 person-days follow up)<br>• 37.6% preventable |
| Forster, 2005[30] (USA) | Community (3 months) | Prospective cohort. Patients discharged home from medical wards. Consent via telephone 2 weeks after discharge. Electronic medical records review and patient telephone survey | Not specified Mean age: 57 years (n=400) | 2 weeks (up to 5 weeks) | 2 hospital doctors. No standardised assessment used | ADE | n=45 (11%)<br>• 27% preventable<br>• 16% ADE re-admission |

Table 1.1 cont. Summary of frequency and types of DRPs in older adults after discharge from hospital

| **Study (country)** | **Setting (duration)** | **Method** | **Patient age (sample size)** | **Post-discharge review period** | **Method of assessment of causality** | **Primary outcome** | **Incidence** |
|---|---|---|---|---|---|---|---|
| Letrilliart, 2001[31] (France) | 305 GP (24 months) | Prospective cohort. All hospital referrals from primary care who had a follow up with the referring GP within 30 days of discharge. GP reported suspected ADR | Not specified Median age: 69 years (n=7540 referrals; n=2227 follow up visits) | 30 days | Consulting GP, reviewed by study GP and hospital doctor, classified by representative of local drug monitoring centre using French intrinsic imputation algorithm | ADR (WHO). Also, harm from discontinuation during admission of a pre-admission drug | n=29 (1.3% of 30-day follow up; 0.4% of all admissions)<br>• 59% preventable<br>• 20% ADR re-admission |
| Gray, 1999[25] (USA) | Community (24 months) | Prospective cohort. Patients discharged from hospital and receiving home health care | ≥ 65 years Mean age: 80.0± 7.3 years (n=256) | 1 month | Naranjo algorithm | ADE | n=52 (20.3%) 1.9% ADE re-admission |

ADE: adverse drug event; ADR: adverse drug reaction; DRP: drug related problem; GP: general practitioner; HMR: home medication review; NR: not reported; USA: United States of America; WHO: World Health Organisation

A sub-section of the literature relating to post-discharge MRH focuses on re-admissions due to MRH.[14,32,33] Hauviller and colleagues'[33] study, conducted in an older population, was a retrospective case note review of patients over the age of 65 years old diagnosed with an ADR on their "index" admission to a Parisian teaching hospital and re-admitted with an ADR during the one year follow up. ADRs were initially identified using International Classification of Disease 10th revision (ICD-10) codes and confirmed through a review of the medical notes. The reported rate of ADR related re-admission was 8.7%.

Overall, few studies have investigated post-discharge MRH, none in older adults in the UK. The incidence of post-discharge MRH varies significantly from 1.3-93% and is largely dependent upon the definition of MRH used and the method used to identify harm.

### 1.2.3 Hospitalisation

The exact prevalence of medication related hospitalisation varies (from 0.1-54%) due to significant heterogeneity in study design, as outlined by Leendertse and colleagues in a literature review of hospitalisation secondary to medication related harm.[34] Whilst acknowledging this variability, a review of the literature over the past 45 years (summarised in Table 1.2) and recent analysis of Hospital Episodes Statistics (HES) data[35] would suggest that the prevalence of ADR related hospitalisation has not improved, and is approximately 5%. Recent studies from the UK suggest higher rates of 6.5% and 8.8%.[2,36]

Table 1.2 Summary of selected literature describing the prevalence of hospitalisation secondary to ADRs

| **Study (year)** | **Aim** | **Databases searched** | **Exclusion criteria** | **ADR definition** | **No. of studies, setting, location** | **Incidence of ADR hospital admissions** |
|---|---|---|---|---|---|---|
| Hakkarainen (2012)[37] | Meta-analysis to estimate the percentage of adult outpatients and inpatients with preventable ADRs and the preventability of ADRs | MEDLINE, EMBASE, Cochrane Library, CINAHL, PsychINFO, IPA, Web of Science (up to Sept 2010) | • Non-English language<br>• Not original research<br>• Non-standard ADR definition<br>• Specific diseases/treatments<br>• Paediatrics or ICU focus<br>• Only life-threatening/fatal ADRs<br>• ADR reported exclusively via spontaneous reporting or diagnostic codes<br>• No assessment or recording of preventable ADR or preventability<br>• Studies where Type A ADRs presumed preventable | WHO or Edward & Aronson (deviation from exact wording accepted as long as functional meaning maintained) | n=22 (14 outpatients, 6 inpatients, 2 both)<br>• Europe (12)<br>• USA and Canada (4)<br>• Iran (3)<br>• Australia (2)<br>• India (1) | All admissions<br>• n=48797 emergency visits/hospitalisations<br>• 2% PADRs (95% CI 1.2-3.2%)<br>• 52% (95% CI 42-62%) preventable |

Table 1.2 cont. Summary of selected literature describing the prevalence of hospitalisation secondary to ADRs

| Study (year) | Aim | Databases searched | Exclusion criteria | ADR definition | No. of studies, setting, location | Incidence of ADR hospital admissions |
|---|---|---|---|---|---|---|
| Kongakew (2008)[38] | Systematic review to estimate the prevalence of hospital admissions associated with ADRs | CINAHL<br>EMBASE<br>MEDLINE<br>(up to Aug 2007) | • Specific conditions or specific type of ADR investigated<br>• Retrospective design<br>• Insufficient data for evaluation of ADR incidence<br>• Non-standard ADR definition | WHO or definition mapped directly to WHO | n=25<br>• Europe (17)<br>• Asia (3)<br>• Australia (2)<br>• USA (2)<br>• South America (1) | All admissions<br>• n=106586<br>• 2143 associated with ADRs<br>• Median 5.3% (IQR 2.7-9.0%)<br>• Range 0.16-15.7%<br><br>All adults (excluding <16 years old)<br>• 620/11477 (median 6.3% [IQR 3.9-9.0%]) admissions associated with ADRs<br><br>Over 60 years<br>• 201/2029 (median 10.7% [IQR 9.6-13.3%]) admissions associated with ADRs |

Table 1.2 cont. Summary of selected literature describing the prevalence of hospitalisation secondary to ADRs

| **Study (year)** | **Aim** | **Databases searched** | **Exclusion criteria** | **ADR definition** | **No. of studies, setting, location** | **Incidence of ADR hospital admissions** |
|---|---|---|---|---|---|---|
| Beijer (2002)[39] | Meta-analysis to establish percentage of ADR related hospital admissions | MEDLINE<br>Cochrane Library<br>(up to Apr 2001) | • Illicit drug use, drug/alcohol abuse<br>• DRPs during admission | WHO | n=68<br>• Australia (15)<br>• Croatia (1)<br>• Denmark (4)<br>• France (3)<br>• Iran (1)<br>• Israel (3)<br>• Italy (2)<br>• Lebanon (1)<br>• S. Africa (1)<br>• Spain (3)<br>• Sweden (1)<br>• Switzerland (1)<br>• Taiwan (1)<br>• USA (25)<br>• Canada (2)<br>• Netherlands (2)<br>• UK (2) | All admissions<br>• n=123794 admission<br>• 6071 associated with ADRs<br>• Mean 4.9±0.1%<br>• Range 0.2-41.3%<br><br>Adults <65 years old<br>• 4082/116241 (mean 4.1± 0.1% [95% CI 0.2-35.1%]) admissions associated with ADRs<br><br>Adults >65 years old<br>• 1251/7553 (mean 16.6±0.8% [95% CI 6.6-41.3%]) admissions associated with ADRs<br><br>>65 years v <65 years significant when adjusted for study size (p=0.005) |

Table 1.2 cont. Summary of selected literature describing the prevalence of hospitalisation secondary to ADRs

| Study (year) | Aim | Databases searched | Exclusion criteria | ADR definition | No. of studies, setting, location | Incidence of ADR hospital admissions |
|---|---|---|---|---|---|---|
| Wiffen (2002)[40] | Meta-analysis of prospective and retrospective studies to estimate incidence of ADRs causing and during hospital admission | MEDLINE (1966–99)<br>EMBASE (1980–99)<br>IPA (1970–99) | Events caused by administration errors, non-compliance, overdose, drug abuse, therapeutic failure, deliberate or accidental self-harm with drugs | WHO | n=69<br>• North America (29)<br>• Europe (31)<br>• Australia/NZ (7)<br>• Middle East (3)<br>• Far East (3)<br>• South Africa (1)<br>• India (1) | All causing and during admission<br>• n=412909 patients<br>• 6072 associated with ADRs<br>• Mean 6.7% (95% CI 6.6-6.8)<br><br>ADRs causing admission only<br>• 133471 admissions<br>• ADR rate 3.1% |
| Lazarou (1998)[41] | Meta-analysis of prospective studies investigating admission due to ADR and inpatient ADRs, focussing on life-threatening and fatal events | MEDLINE (1966–96)<br>EMBASE<br>IPA<br>Science citation index | • Specific conditions or type/drug exposure<br>• Insufficient data to evaluate ADR incidence<br>• Possible ADRs (defined by Karch and Lasagna)<br>• Non-US studies<br>• Retrospective studies<br>• No English translation | WHO | n=39 (USA only) | All admission<br>• n=45770 admission<br>• serious 4.7% of 28017 (95% CI 3.1-6.2%)<br>• fatal 0.13% of 17753 (95% CI 0.04-0.21%) |

Table 1.2 cont. Summary of selected literature describing the prevalence of hospitalisation secondary to ADRs

| Study (year) | Aim | Databases searched | Exclusion criteria | ADR definition | No. of studies, setting, location | Incidence of ADR hospital admissions |
|---|---|---|---|---|---|---|
| Einarson (1993)[42] | Identify the prevalence of drug related problems causing hospitalisation | MEDLINE (1966–89) Index Medicus IPA | • Non-English language<br>• Admission due to overdose/intentional poisoning, attempted suicide, drug abuse or intoxication | Definition by Cluff - any unintended/undesired consequence of drug therapy.<br>Also, non-compliance (deviation from prescriber's regimen including over/undercompliance) | n=37 (49 reports of ADR related admission rates)<br>• North America (30)<br>• Europe (10)<br>• Asia (5)<br>• Australasia (2)<br>• Africa (2)<br><br>All large hospitals (mainly urban teaching) | All admissions<br>• n=69187 admissions<br>• 2897 (4.2% [range 0.2-21.7%]), (median 4.9% [IQR 2.9-6.7%]), (mean 5.5±4.1%) due to ADR<br>• Meta-analytic average 5.1% (95% CI 4.4-5.8%)<br>• Study sample size 41-11891 (median 714 [IQR 275-1245]), (mean 1412±2233)<br>• 25% had more than one ADR |

ADR: adverse drug reaction; CI: confidence interval; CINAHL: Cumulative Index to Nursing and Allied Health Literature; ICU: intensive care unit; IPA: International Pharmaceutical Abstracts; NZ: New Zealand: PADRs: preventable adverse drug reactions; USA: United States of America; WHO: World Health Organisation

### 1.2.4 Impact of MRH

Irrespective of the variation in the overall incidence and prevalence of MRH and associated inconsistency in terminology, it is universally reported that older adults are more likely to experience serious harm from their medicines resulting in hospital admission than younger adults.[2,36,38,39,43] As the largest consumers of healthcare and most rapidly growing section of society, tackling MRH in older adults is a national priority. The 2013 report from the House of Lords Select Committee on Public Health and Demographic Change, Ready for Ageing, concluded that the current healthcare system is not delivering "good enough healthcare and is inefficient. The Government and our society are woefully underprepared for the rapid ageing of the UK population".[44]

This demographic transition is a global phenomenon describing the shift from high fertility, high mortality to low fertility, low mortality. Consequently, the global population is ageing. By 2050, there will be over 2 billion people over the age of 60 in the world.[45] At present, one person in six in the UK is over the age of 65 years.[46] Whilst improvements in healthcare and social development have supported an increased life expectancy, lifestyle changes involving high dietary intake of fats, sugars and salt, smoking and alcohol consumption have resulted in an increase in chronic disease.[47] Over 50% more people will be living with three or more long-term conditions (LTCs) in England in 2018 compared to 2008.[44] An analysis conducted in Scotland using data from 2007 identified that most people over the age of 65 years were multimorbid (see Figure 1.2). Interestingly, in absolute terms more people under the age of 65 years old were multimorbid than those over 65 years old, however older people had more comorbidities on average.[48] This observation has implications for the delivery of care to older people in the future who are likely to present with increasingly complex multimorbidity as they age.

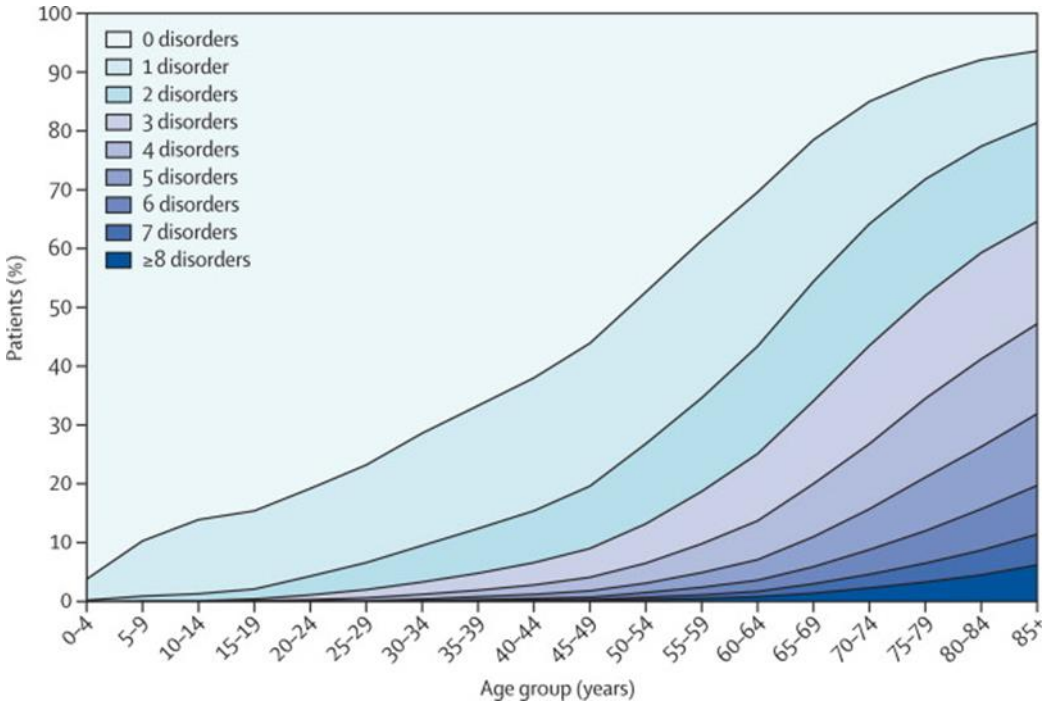



Figure 1.2 Number of chronic disorders by age group (Barnett et al. Epidemiology of multimorbidity and implications for health care, research and medical education: a cross-sectional study[48])

The fragmented care that is associated with multimorbidity can increase an individual's risk of experiencing harm.[49] Often seen by a specialist for each condition, in addition to their GP, older patients frequently have multiple healthcare professionals responsible for the prescribing of their medicines which has been demonstrated to increase their risk of MRH.[26] Moreover, each condition is likely to have its own specific guideline outlining the recommended pharmacological management which leads to complex polypharmacy that is difficult to manage and potentially harmful.[50]

## 1.3 Risk of medication related harm

The increased incidence of MRH experienced by older adults is likely to be multifactorial, with age related changes in physiology, compounded by chronic disease, affecting drug pharmacology. Furthermore, the aforementioned polypharmacy driven by guideline based prescribing and potential for non-adherence are also likely to increase the risk of MRH.

### 1.3.1 Changes in drug pharmacology

The physiological changes that occur in old age can impact on drug pharmacokinetics and pharmacodynamics (Table 1.3 and Table 1.4) resulting in an increased susceptibility to medication related harm due to unpredictable and enhanced effects.[51] It is also important to consider the impact of co-morbidities and polypharmacy causing drug-disease and drug-drug interactions which alter drug pharmacokinetics, for example heart failure which may result in a reduction in drug absorption due to mucosal oedema as well as changes in renal clearance, due to changes in renal blood flow.

Table 1.3 Examples of age-related physiological changes and the impact on drug pharmacokinetics

| **Physiological change** | **Impact on pharmacokinetics** | **Drug example** |
|---|---|---|
| Changes to active transport | Reduced absorption of some drugs through active transport | Vitamin B12, iron, calcium |
| Reduced dopa-decarboxylase in gastric mucosa | Increased absorption of levodopa | Levodopa |
| Reduced liver mass and liver blood flow | Increased bioavailability of drugs with extensive first-pass metabolism | Propranolol, labetalol |
| | Reduced activation of pro-drugs activated in the liver | Enalapril, perindopril |
| | Reduced clearance of drugs with high hepatic extraction ratio | Glyceryl trinitrate, propranolol |
| Relative reduction in total body water | Reduced volume of distribution and increased serum concentrations of water-soluble drugs | Gentamicin, digoxin |
| Relative increase in body fat | Increased volume of distribution and longer half-life of lipid-soluble drugs | Diazepam, lidocaine |
| Reduced serum albumin concentration* | Reduced protein binding so increased concentration of free (active) drug | Warfarin |
| Reduction in glomerular filtration rate | Reduced drug clearance of renally excreted drugs | Water-soluble antibiotics, diuretics, digoxin, lithium, NSAIDS |

Adapted from Alder et al.[51]

*clinical relevance of this in ageing is limited, with the possible exception of acutely ill frail patients.

Table 1.4 Examples of age-related changes in drug pharmacodynamics

| Drug | Pharmacodynamic effect | Age-related change |
|---|---|---|
| Diazepam | Sedation, postural sway | Increased |
| Diltiazem | Antihypertensive effect | Increased |
| | Acute PR interval prolongation | Reduced |
| Furosemide | Peak diuretic response | Reduced |
| Isoprenaline | Chronotropic effect | Reduced |
| Morphine | Analgesic effect | Increased |
| | Respiratory depression | Unchanged |
| Temazepam | Postural sway | Increased |
| Warfarin | Anticoagulant effect | Increased |

Adapted from Alder et al.[51]

### 1.3.2 Polypharmacy

As already outlined, increasing multimorbidity is associated with an increasing number of prescribed medicines resulting in the publication of major policy documents from across the United Kingdom, including: The King's Fund, Polypharmacy and medicines optimisation[52]; the All Wales Medicines Strategy Group, Polypharmacy – Guidance for prescribing in frail adults[53] and; National Health Service (NHS) Scotland: Polypharmacy guidance.[54] Over the course of a decade the number of items prescribed in the general population increased by 53.8% from 11.9 (2001) to 18.3 (2011)[55], with a particularly high proportion (16.4%) of patients (in 2010) over the age of 65 years old receiving 10 or more medicines[56]. This figure may have increased over the past seven years and so a simple drug count, whilst easily identifiable in clinical practice, can become quickly outdated. It has therefore become common practice to think of polypharmacy in terms of the number of inappropriate medicines prescribed based on specific criteria such as Beer's[57] or the Screening Tool of Older People's potentially inappropriate Prescriptions (STOPP) and the Screening Tool to Alert doctors to the Right Treatment (START)[58]. Polypharmacy, whether measured by medicine count or specific criteria is consistently associated with a higher rate of MRH.[12,14,59–64]

### 1.3.3 Drug classes

Certain drug classes seem to be more frequently associated with MRH irrespective of the study setting, for example drugs used in cardiovascular disease (including anticoagulants) accounted for 47% of ADRs 30 days post-discharge, and central nervous system (CNS) drugs (including

psychoactive drugs and opioids) for 20%.[31] A systematic review of studies investigating hospital admissions associated with ADRs in adults identified 10 studies, 8 of which reported the types of medicines. Cardiovascular medicines (45.7%), non-steroidal anti-inflammatory drugs (NSAIDs) (14.6%) and central nervous system agents (9.7%) were the groups of medicines most commonly involved in adult ADR, and also when a sub-analysis of the studies involving only older adults was conducted.

### 1.3.4 Non-adherence

Adherence to long term treatments is estimated to be around 50%[65] and is associated with poor health outcomes, accounting for between one and two thirds of hospital admissions in the USA[66]. A study, by Col and colleagues, of 315 patients over the age of 65 years admitted consecutively to acute care, identified that 89 (28.2%) admissions were medicines related, 36 (11.4%) of which were due to non-adherence. Non-adherence was defined as "any nontrivial deviation from the prescribed medication regimen (as judged by the research team). It includes dosage errors (underuse and overuse), interruption of treatment, failure to take drugs at specified times, taking them at incorrect intervals, and/or the addition of other drugs." Factors significantly associated with non-adherence were living alone, using two or more "when required" medicines, having no assistance with their medicine and using multiple pharmacies.[67] Published in 1990, it is likely that this is a conservative estimate of harm due to non-adherence due the study population differing to today's older population. The mean number of medicines was 4, far less than that reported in more recent observational studies.[68] This is important because in older adults non-adherence is often thought to be unintentional due to poor cognition for example but in reality half of all non-adherence in older adults is intentional[71] with one of the driving factors being polypharmacy and regimen complexity[69].

Given the awareness of the risk factors described, what has been done already to reduce the potential harm from medicines in older adults?

## 1.4 Reducing medication related harm

A large proportion of MRH is reported to be preventable[26] which has resulted in the development of various strategies aiming to reduce the incidence, including the concept of medicines optimisation. Defined as "a person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines"[72], it recognises the potential for poor medicines related outcomes and proposes processes such as medicines reconciliation (MR) and medicines reviews to overcome them.

### 1.4.1 Medicines reconciliation

Launched in 2004 as part of the US Institute of Healthcare Improvements "100,000 Lives Campaign", MR is a process that aims to reduce harm caused by medication errors during the transition of care.[73] A key component of the National Institute for Health and Care Excellence (NICE) Medicines Optimisation guidelines[72], this process has been fully adopted by secondary care in the UK. Within 24 hours of admission all patients have their pre-admission medicines list reviewed against their current medicines list and any discrepancies rectified. "Medicines" include over-the-counter and herbal medicines. This process should be repeated when a patient transfers within the hospital and also into primary care following discharge from hospital. There does not however appear to have been the same uptake in primary care[74], even though there is evidence to suggest it can reduce post-hospital healthcare utilisation due to ADEs[75].

### 1.4.2 Medicines reviews

In the UK, medicines reviews have been part of the General Medical Service contract[76] and an advanced service within the Pharmacy contract[77] for over a decade. They exist at four levels: Level 0 – Ad hoc (an unstructured, opportunistic review); Level 1 – Prescription review (a technical review of a list of patients' medicines); Level 2 – Treatment review (a review of medicines with the patient's full notes) and; Level 3 – Clinical medication review (a review of the patient, illnesses and drug treatment during a consultation).[78] As experts in medicines, pharmacists are ideally placed within the multi-disciplinary team to review medicines with the aim of preventing harm. Indeed, a recent study demonstrated that their presence on the general medical ward round resulted in a reduction of preventable ADEs from 26.5 to 5.7 per 1000 hospital days.[79] In primary

care, many community pharmacists offer the medicines use review (MUR) service which aims to identify any problems or information needs that a patient has with regards to their medicines[80], but the impact of these reviews on MRH is unclear. Recognised as a priority group, older patients recently discharged from hospital are a target group for MURs but the uptake of the service has been varied and data to suggest benefit is limited.[81] Recently, as part of the General Practice Forward Review 2016[82] in England, additional funds have been made available to general practices to employ clinical pharmacists as core members of their workforce. Part of their role will be to support patients with long term conditions using multiple medicines, which will include medicines reviews. Whilst initial outcomes of the evaluations appear positive, including pharmacists supporting medicines optimisation and the management of the long term conditions[82], the impact on MRH is unknown.

### 1.4.3 Prescribing indicators

Another systems based approach to reducing MRH is through the application of a list of implicit or explicit prescribing indicators, such as the Medicines Appropriateness Index[83] or the STOPP/START criteria[58] where pharmacological appropriateness is monitored. Although an association between ADRs and the prevalence of prescribing potentially inappropriate medicines has been demonstrated, the ability to predict the risk of a future event has not yet been confirmed. A large public health database review conducted in the USA identified that “high-risk medicines”, as definited by the Beer’s Criteria, contributed to a small proportion of emergency hospital admission due to an adverse drug event. Beer’s Criteria medicines were associated with only 6.6% of admissions, over half of which were due to digoxin.[43] Furthermore, this focus on specific medicines often restricts, due to formulary and licensing issues, the use of such prescribing indicators in an international context. A further limitation of such an approach is that they are time-consuming to use in routine care and can be viewed, due to the focus on medicines, as one dimensional. From the literature, MRH appears to be a multi-dimensional challenge, comprising broadly of medicine (Table 1.5), clinical (Table 1.6) and social (Table 1.7) risk factors.

Table 1.5 Examples of medicines related risk variables for MRH (ADR or ADE) in >60 year olds

| **Medicines related risk variables** | | |
|---|---|---|
| **Significant (univariate analysis)** | **Significant (multivariate analysis)** | **Not significant** |
| **Number of medicines** | | |
| Polypharmacy[26,64,84–86] | Polypharmacy[26,64,84–86] | Polypharmacy[25,87] |
| ≥5[18,64], ≥7[88], ≥12[30] medicines | ≥5[18,64], ≥7 [88], ≥12[30] medicines | |
| **Individual medicines** | | |
| Warfarin[26] | Warfarin[26] | Warfarin[87] |
| Digoxin[85,89] | Digoxin[89] | Digoxin[87] |
| | | Theophylline[26] |
| **Classes of medicines** | | |
| ACE inhibitors[85,89] | Antibiotics[64] | Alzheimer's treatments[64] |
| Antibiotics[64,85] | Anticoagulants[26] (a)[88] | Anticholinergics[26] |
| Antihypertensives[85,88] | Antipsychotics[64,88] | Anticonvulsants[87] |
| Anticoagulants[26,64] (a)[88] | Antidepressants[64,89] | Antigout[64] |
| Anticonvulsants[64] | Beer's criteria[86] | Antihistamines[64] |
| Antipsychotics[64,88] | Hypnotics/sedatives (d)[26] | Antineoplastics[64] |
| Antidepressants[64,88,89] | Hypoglycaemic agents[85] | Antipakinsonians[64] |
| Beer's criteria[86] | Nutrients/supplement (d)[64] | Antipsychotics[26] |
| Benzodiazepines [26] | | Beer's criteria[87] |
| Beta-blockers[85] | | Benzodiazepines[87] |
| Cardiovascular[64] | | Cholesterol-lowering[64] |
| Hypnotics/sedatives[64] (d)[26] | | Diuretics[64] (loop diuretics[87]) |
| Hypoglycaemic agents[64,85,89] | | Gastrointestinal[64] |
| Muscle relaxants[64] | | High-risk non-Beer's[87] |
| Non-aspirin NSAIDs[26] | | Hypoglycaemic agents[87] |
| Nutrients/supplement (d)[64] | | Non-opthalmic topicals[64] |
| Opioid analgesics[85] | | Non-opioid analgesics[64] |
| Tricyclic antidepressants[26] | | Opioid analgesics[26,64] |
| | | Opthalmics[64] |
| | | Osteoporosis[64] |
| | | Respiratory[64] |
| | | Steroids[26,64] |
| | | Thyroid[64] |
| **Other** | | |
| New medicine[25,87] | New medicine[25] | MR on admission[32] |
| Previous ADR[18,89] | Previous ADR[18] | Previous ADR[26,86] |
| Multiple prescribers[26] | | |

(a): within past 3 months; (d): reduced risk; MR: Medicines reconciliation; NSAIDs: non-steroidal anti-inflammatory drugs

Table 1.6 Examples of clinical related risk variables for MRH (ADR or ADE) in >60 year olds

| **Clinical related risk variables** | | |
|---|---|---|
| **Significant (univariate)** | **Significant (multivariate)** | **Not significant** |
| **Co-morbidities** | | |
| CVD[88] (d)[89] | CKD (c)[18] | CCF[33,87] |
| Respiratory disease[88] | CCF[18] | CKD[26,33,64,86,87] |
| Recent VTE (a)[88] | Liver disease[18] | Dementia[18,26,33,64,86] |
| CKD (c)[18] | Experiences angina (d)[89] | Anaemia[18] |
| CCF[18] | Experiences COPD[89] | Diabetes[18,33] |
| Liver disease[18] | GI problems[89] | COPD[18] (lung disease[33]) |
| Diabetes[85,89] | Hyperlipidaemia[85] | Depression[18,25] |
| Endocrine disorders[89] | Fall (d)[64] | Falls[18,86] |
| Haematological disorders[89] | Neoplasm[33] | Liver disease[33,64,86] |
| Hyperlipidaemia[85] | | BMI[18] |
| Infection (d)[89] | | PVD[33] |
| PUD[89] | | Stroke[33] |
| Osteoarthritis/arthritis[85] | | Paraplegia[33] |
| Neoplasm[33] | | Connective tissue disease[33] |
| Metastatic cancer[33] | | Acute MI[33] |
| **Biochemistry** | | |
| Abnormal potassium[89] | Abnormal potassium[89] | Albumin <3.5g/dl[18] |
| High WBC[85] | High WBC[85] | |
| **Collective co-morbidities** | | |
| No. of co-morbidities[86], ≥4[18] | ≥4 co-morbidities[18] | No. of co-morbidities[26,87] (d)[88] |
| High CIRS index[64] | | Physical co-morbidity[84] |
| CCI ≥5[64] or ≥1[33] | | Psychiatric co-morbidity[84] |
| | | Geriatric conditions[87] |
| **Reason for admission** | | |
| Bleeding (including rectal)[89] | | |
| Dehydration[89] | | |
| Dizziness/vertigo[89] | | |
| GI disorder[89] | | |
| Hyper/hypoglycaemia[89] | | |
| Abnormal glucose[89] | | |
| Chest pain (d)[89] | | |

(a): within past 3 months; (c): eGFR<60ml/min; (d): reduced risk; BMI: body mass index; CCF: congestive cardiac failure; CCI: Charlson comorbidity index; CIRS: cumulative index rating scale; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; GI: gastrointestinal; GI disorders :gastrointestinal disorders (nausea, vomiting, diarrhoea); Geriatric conditions: cognitive impairment, depression, visual impairment, incontinence, constipation, falls, gait instability; MI: myocardial infarction; PVD: peripheral vascular disease; PUD: peptic ulcer disease; VTE: venous thromboembolism; WBC: white blood cells

Table 1.7 Examples of social (and other) related risk variables for MRH (ADR or ADE) in >60 year olds

| **Social (and other) risk variables** | | |
|---|---|---|
| **Significant (univariate)** | **Significant (multivariate)** | **Not significant** |
| Length of stay[85,86] | Length of stay[85] | Outpatient geriatric clinic visits in previous year[84] |
| New resident[64] | New resident[64] | Primary care visits in previous year[84] |
| Thinks drug were responsible for admission[89] | Thinks drug were responsible for admission[89] | A&E attendances in previous year[84] |
| Medicine cost[67] | Type of insurance[67] | Hospitalisation in previous year[84] |
| Pharmacy consultation[32] | Pharmacy consultation[32] | Days to re-admission[32] |
| No. of pharmacies used[67] | | IADLs disability[18,25,64,86,87] |
| Discharge counselling on side effects (d)[30] | Discharge counselling on side effects (d)[30] | |
| **Demographics** | | |
| Age(d)[33] | Age[32] | Age[18,25,64,84,86,87,89] (>75 years[26]) |
| MMSE[25] | MMSE[25] | Marital status[84] |
| Gender[25] | Gender[25] | Gender[33,64,86,88,89] |
| Missed follow up[32] | Missed follow up[32] | Ethnicity[87] |
| | | Self-reported health score[25,87] |
| | | Smoker[18,89] |
| | | ETOH consumption[25,86] |
| | | Level of education[32,86] |
| | | Lives alone[25] |

A&E: accident and emergency; (d): reduced risk; ETOH: alcohol; IADLS: instrumental activities of daily living; MMSE: mini mental state examination

### 1.4.4 Identification of high-risk patients

Other approaches in health care have overcome the multi-dimensional nature of clinical risk. In these approaches predicting the risk of developing specific conditions is a routine component of everyday medicine, for example, the European Society of Cardiology $CHA_2DS_2VASc$ score for determining stroke risk in patients with atrial fibrillation.[90] Preceded by $CHADS_2$, this updated score more accurately identifies those at low stroke risk through inclusion of non-clinical risk factors (gender and age ranges), in addition to medical co-morbidities such as heart failure, hypertension and previous stroke. With a healthcare system under increasing financial pressure it is perhaps understandable that risk prediction models are generating increasing interest[91], however the surge of risk prediction research has been described as “low quality, low impact”.[92] A quality risk stratification model could assist in case prioritisation, supporting clinicians and patients to make informed decisions about treatments, and deliver a more efficient healthcare

service. Where current systems only look at the medicines aspect of risk, a risk prediction model may be able to map the complex interplay between clinical, social and medicine related variables, and stratify an individual's risk of a future adverse drug event.

Experts in the field define risk prediction, or prognostic modelling, as "the probability/risk of an individual developing a particular state of health (outcome) over a specific period of time, based on his or her clinical and non-clinical profile".[93] Clinical profile may include such things as renal function or number of medicines, but from a review of the variables it seems that these alone do not produce accurate enough predictions. The non-clinical aspect of the patient profile seems to be understudied in this population and may be the missing element when trying to accurately identify those at risk of MRH, especially during the post-discharge period. It is necessary to consider the whole individual when prognosticating[93] and all the complexities that are associated with that individual, especially in a complex older population and so aspects such as social support or adherence may be worth further investigation. A quality prediction model, that incorporates the intricacies of MRH in older adults, should accurately identify patients at high-risk of harm.

## 1.5 Conclusion

Older adults have a high-risk of MRH due to the physiological changes that occur with ageing and the consequential altered drug handling, in conjunction with high levels of multimorbidity and associated polypharmacy. During acute illness, and following discharge from hospital, older adults are particularly vulnerable to the potential harmful effects of their medicines. Yet the post-discharge period is a stage of the patient journey that has received little attention from researchers. Several systems based approaches aimed at optimising medicines use have been developed with limited success, and with the unprecedented growth in the number of multimorbid older people in our society the practical utility of these time-consuming interventions is questionable. Risk stratification is a potential solution to targeting interventions at those who are at highest risk of harm thereby improving the efficiency of the healthcare service, however further research is required to determine if it is possible to identify older patients at risk of MRH following an acute hospital episode. This forms the main aim of this thesis which is outlined in more detail in Chapter 2.

# Chapter 2 Thesis overview

## 2.1 Importance of this work

Evidence from the literature demonstrates that clinicians are being presented with an increasingly complex ageing population. The majority of people over the age of 65 years old live with multiple chronic conditions for which they receive a complicated array of medicines, the consequences of which in the older inpatient population has been extensively described. Similarly, hospitalisation of older adults due to their medicines is well documented. An area which has received little attention are the weeks immediately after discharge from hospital following an acute admission, during which time individuals may be described as having "post-hospital syndrome"[23]. Defined as "an acquired, transient condition of generalised risk"[23], post-hospital syndrome describes the depletion of homeostatic reserves due to the stress of the hospital admission, as much as the impact of the original acute illness, resulting in an increased vulnerability to harm. Factors relating to a depleted physiological reserve as a consequence of hospital admission may therefore contribute to the risk of MRH through, for example, altered drug handling or a limited capacity to cope with the pharmacological effects of a new medicine. Moreover, depletion of psychosocial reserves is also likely to play a significant role in post-discharge MRH, however the impact of this group of factors, for example mood or package of care, is poorly understood.

The lack of evidence around the post-discharge period poses a problem when attempting to design and deliver interventions to advance the care of older adults. This research will help to quantify the harm older adults experience from their medicines when they leave hospital but, more importantly, it will assist in the identification of those most at risk of harm so that interventions can be targeted. During a time of increasing financial pressures in the National Health Service (NHS), the ability to allocate resources to those most at risk of harm would benefit both the patients and the organisation. Through a series of studies outlined in this chapter, this thesis will further our understanding of medication related harm (MRH) in older adults and so assist in the improvement of future care.

## 2.2 Research aim and objectives

This thesis aims to examine the possibility of identifying older patients at risk of medication related harm following discharge from hospital. It will do this by:

1. Systematic review of the literature to identify, and assess the quality of, validated medication risk prediction models to determine their potential benefit to the care of older people
2. Exploration of medication related harm experienced by older adults following discharge from an acute inpatient episode in a UK hospital
3. Exploration of the relationships between physiological and psychosocial variables and the risk of post-discharge medication related harm.

## 2.3 Description of thesis chapters

The first chapter of this thesis summarises the findings of the literature around MRH. In particular, it highlights the multiple definitions and methods of measurement used in this research area, and the consequential variation in the reported incidence. The risk factors associated with, and the consequences of, MRH in older adults are discussed in the context of an ageing, multimorbid population and a health service under growing pressures to increase efficiency. Current approaches, and their limitations, to managing the risk of harm from medicines in older adults are described. Potential future strategies in the form of risk stratification are outlined with a focus on the post-discharge period, a high-risk time in the patient journey which has been seldom studied in the UK.

The following section provides a brief outline of the three studies conducted (Figure 2.1) as part of this research and their location within the thesis.

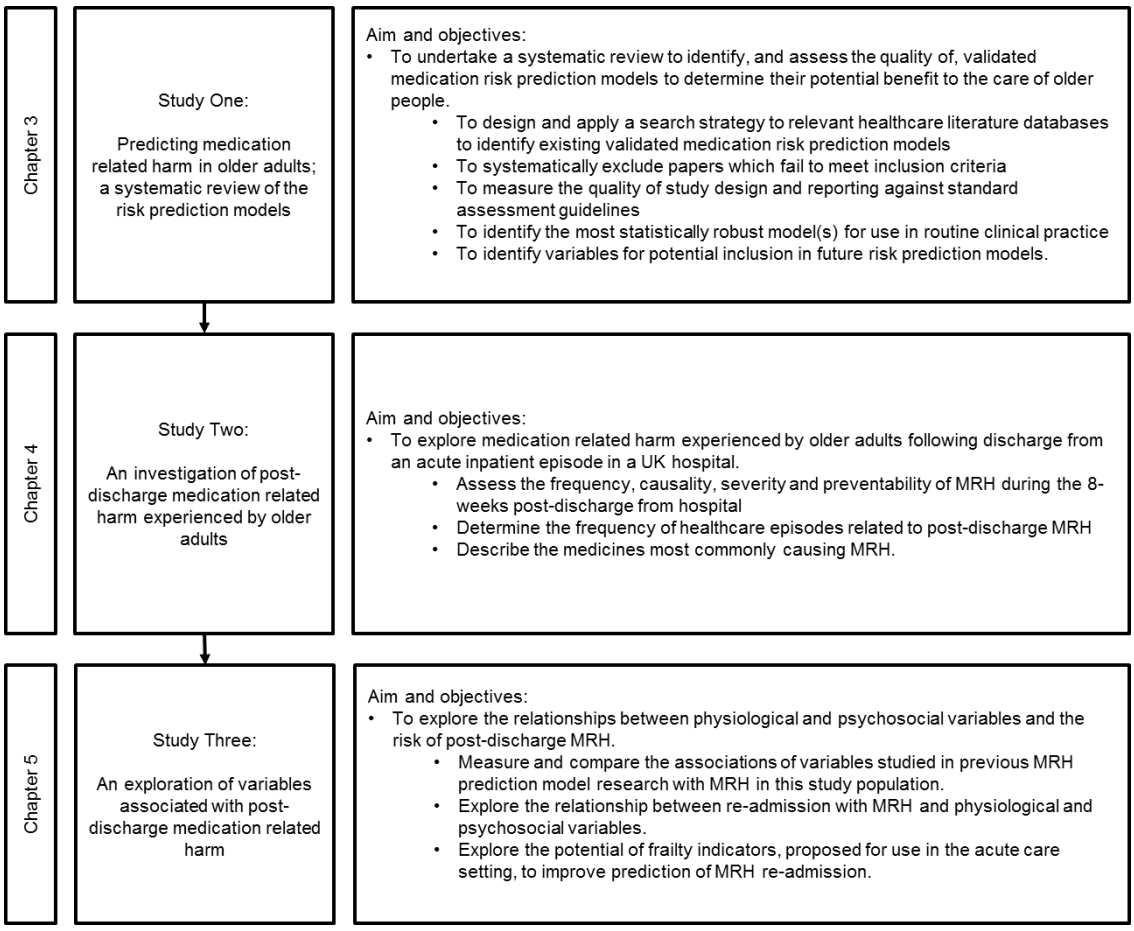



Figure 2.1 Overview of research presented in this thesis

Chapter 3 provides a detailed outline of the key stages of developing, validating, measuring the impact and implementation of a quality risk prediction model. Through a systematic review of the literature (Study 1), the chapter then identifies existing MRH risk prediction models and assesses their quality. This study was published in Clinical Interventions in Aging (Stevenson JM et al. Predicting adverse drug reactions in older adults; a systematic review of the risk prediction models. Clin Interv Aging. 2014 Sep; 1581 - see Appendix A). This study was designed to identify prediction models but through a detailed critique of the studies it also informed the design of Study 2 and the development of a conceptual framework, presented at the end of the chapter. The conceptual framework outlines the complexity of MRH in an older population and reflects upon the parallels with frailty and the need to consider a broad range of variables in order to identify those at risk.

Chapter 4 provides detail of the findings of an observational study (Study 2) undertaken to gain an understanding of the incidence, severity, preventability and causality of post-discharge MRH.

The body systems affected and most common type of medicines involved in MRH were reported along with the proportion of harm that was due to an ADR, non-adherence or a combination of both. Healthcare utilisation was also measured. The full protocol for this study was published in BMC Geriatrics (Stevenson JM et al. Protocol for a Prospective (P) study to develop a model to stratify the risk (RI) of medication (M) related harm in hospitalized elderly (E) patients in the UK (The PRIME study). BMC Geriatr. 2016;16:22 – see Appendix B). The study identified a frail population and a higher than anticipated re-admission rate which directed subsequent analysis in Study 3.

Chapter 5, using data collected in Study 2, explores the relationships between a range of variables and post-discharge MRH. In Study 3, previously studied variables, along with variables suggested through the conceptual framework, are analysed and the findings discussed. Due to the high re-admission rate, a sub-analysis of re-admissions was conducted with the aim of identifying variables that would predict re-admission due to MRH.

A final discussion, summarising the findings of this research in the context of the current published literature is provided in the last chapter, Chapter 6. Recommendations for practices and further work are also outlined.

## 2.4 The research team

The main research team consisted of five members; two principal investigators, the principal researcher (Jennifer Stevenson), a research pharmacist and research nurse. The principal researcher was responsible for the study design, training of staff and day to day research co-ordination, overseen by the principal investigators.

In Study 1 the principal researcher designed and ran the search strategy for the systematic review. Titles and abstracts were independently reviewed by the principal researcher and a medicines information specialist pharmacist and papers to be included agreed through discussion. Data were extracted from the studies meeting the inclusion criteria by the principal researcher and confirmed by two independent reviewers (a medicines information specialist and a professor of medical statistics). The quality assessment of the included studies was conducted

by the principal researcher and medicines information specialist and confirmed by experts in medical literature review and clinical geriatrics.

Recruitment of patients to the observational study (Study 2) was conducted mainly by the research nurse, with the support of the research pharmacist, both under the supervision of the principal researcher. Follow up was conducted by the principal researcher with the support of the research pharmacist. Classification and categorisation of MRH was conducted by the principal researcher and principal investigators.

## 2.5 The PRIME Study

This thesis focusses on a sample of patients recruited from one hospital, St. Thomas' Hospital, participating in a larger multi-centre study, the PRIME Study. The PRIME Study, with the aim of developing a risk prediction model to identify older patients at risk of MRH in the 8-week period following hospital discharge, was conducted in 5 teaching hospitals in the South East of England. A sample size calculation, based on the nomogram designed by Carley and colleagues[94] and Buderer[95], estimated 1500 patients would be required to achieve a sensitivity of 80% with a 95% confidence interval width of 5%, based on a MRH prevalence of 30%. Furthermore, this would allow a maximum 45 variables to be tested for inclusion in the risk prediction model whilst adhering to the commonly applied 10 events per variable rule of risk prediction modelling[96–98]. The PRIME Study monitoring committee identified that the St. Thomas' cohort had a re-admission rate almost three times higher than the other sites in the PRIME Study and so a sub-analysis of this population was conducted. This thesis reports the results of this sub-analysis.

The principal researcher (Jennifer Stevenson) developed the study documentation, including patient information leaflets (see Appendix E and Appendix F), consent forms (see Appendix G and Appendix H) and training documents (Appendix I).

# Chapter 3 Systematic review

## 3.1 Introduction

Predicting the risk of developing specific conditions is already a routine component of everyday medicine, for example the European Society of Cardiology $CHA_2DS_2$-VASc score for determining stroke risk in patients with atrial fibrillation.[90] More generally, with a focus on long-term conditions (LTCs), risk prediction models, for example the John Hopkins University Applied Clinical Guideline System, have been adopted by the Primary Care Sector of the NHS[99,100] to identify patients at risk of hospital admission. It is perhaps understandable that prediction models that quantify the risk of ADRs occurring in older patients are generating increasing interest as readmissions are more frequent, and are associated with financial consequences.[101] The 2013 report from the House of Lords Select Committee on Public Health and Demographic Change, *Ready for Ageing*, concluded that the current healthcare system is not delivering "good enough healthcare and is inefficient. The Government and our society are woefully underprepared for the rapid ageing of UK population". The committee called for the provision of better healthcare in a more efficient manner.[44]

In the UK, one person in six is over the age of 65 years.[46] The King's Fund has projected that there will be over 50% more people with three or more LTCs in England in 2018 compared to 2008.[44] As a direct result, there is likely to be an increase in the number of medicines prescribed to treat LTCs leading to polypharmacy, a frequently reported risk factor for ADRs.[12,14,61–64] We also know that the changes in drug pharmacokinetic and pharmacodynamic properties that occur with ageing often lead to an increased susceptibility to ADRs.[102] Therefore, given the awareness of potential risk factors, the ability to stratify a patient's risk of suffering an ADR is attractive. Risk stratification could assist in case prioritisation, supporting clinicians and patients to make informed decisions about treatments and deliver a more efficient healthcare service.

To predict risk in the clinical setting accurately, a quality risk prediction model should be the result of four key stages, namely: development, validation, impact and implementation.[91,93,103,104] A description of each stage, and its importance, is provided in Table 3.1.

Table 3.1 Description of stages of multivariable prognostic research

| Stage | Description of stage | Importance |
|---|---|---|
| Development | • Identification of the important predictors.<br>• Assignment of relative weights to each predictor.<br>• Estimation of model's predictive ability (calibration and discrimination).<br>• Estimation of potential for optimism using internal validation techniques.<br>• Adjustment of model for overfitting, if necessary. | Identification of variables, in a combination, that accurately identify those at risk of the outcome. |
| Validation | • Testing the model's predictive performance (calibration and discrimination) in new participants.<br>• Can be narrow – using participants from same institution, measured in the same way and by the same researchers at a later time (internal validation), or in another single institution by different researchers using slightly different definitions and data collection methods (external validation).<br>• Can be broad – using participants from various other institutions or using wider inclusion criteria. | Gives understanding about the model's ability to perform in a different patient group from that of the development population. |
| Impact | • Quantifying whether the use of a prognostic model in the clinical setting by practicing healthcare professionals truly improves decision making and patient outcomes.<br>• Can be narrow – within same institution etc.<br>• Can be broad – in a different institution etc. | Demonstration of model's value within the healthcare setting. |
| Implementation | • Applicable when a model is consistently accurate in diverse populations.<br>• Demonstration of superior ability to discriminate in comparison to routine care (ideally conducted during development phase).<br>• Assessment of face validity and user-friendliness. | Support routine application in clinical care setting. |

Adapted from Moons and colleagues[93] and Toll and colleagues[91]

It is recognised that many risk prediction models are often only the product of the first two stages, the methods and outcomes of which are frequently poorly reported.[91,104–106] Furthermore, to be of practical use, these models should ideally use clearly defined, easily obtainable data, have good predictive power, be tested in a large sample representative of the target population and have high reliability and face validity.[91]

The ideal study design is summarised in Table 3.2, with key aspects explained in more detail in the following paragraphs.[107–110]

Risk factors of interest, also referred to as candidate predictor variables, may include demographics e.g. age or gender, blood biochemistry, clinical diagnoses, the results of genomic investigations amongst many other possible variables. Candidate predictor variables should be identified through a review of the literature and expert opinion. Univariate analysis of variables collected from the development cohort may be used to identify candidate predictor variables however, using this method alone may result in a sufficiently accurate model within the study population but poor performance when applied elsewhere. Where this occurs, the model may be said to be overfitted to the development population and will likely have poor generalisability. Furthermore, candidate predictor variables should be clearly defined to allow replication of the study in external populations by other investigators.[111]

Outcomes must also be clearly defined and a standardised method of measurement utilised. This is especially important when considering the area of MRH where multiple definitions exist for ADR and are often used interchangeably with ADE.

The design should ideally be a longitudinal prospective cohort study to ensure that all predictors and outcomes are captured and thus limiting missing data. Whilst retrospective data sets may be used, there is often a challenge with incomplete data and variation in predictor and outcome measurement. Where a prospective method is applied, investigators should be blinded to the candidate predictor variables, and the outcome, to limit bias.[111]

Table 3.2 Criteria to consider when evaluating the quality of risk prediction models

| **Standard criteria[a]** | **Explanation** | **Example** |
|---|---|---|
| Study design | Prospective: allows optimal collection of potential candidate variables; smaller dataset often generated.<br>Retrospective: enables use of large previously collected datasets; quality of candidate variable data may be compromised due to missing data which rarely occurs at random. | Prospective, n=690, all exclusions were for appropriate reasons [85]<br>Retrospective, n=5936, unknown number exclusions due to missing data.[112] |
| Participant recruitment | Inclusion and exclusion criteria should be clearly described to allow full assessment of patient population studied.<br>Any systematic variation in recruitment of patients should be viewed with caution due to risk of sampling bias.<br>There is no pre-determined satisfactory number for loss to follow up however it should be considered that missing data impacts on the statistical power of study. | Interview data were only collected for half of the patients during the development phase. Patients not wishing to participate in the interview may systematically differ.[89] |
| Candidate predictor variables | Variables and their measurement should be clearly defined to allow replication.<br>Investigators should be blind to the outcome to reduce the risk of bias.<br>Continuous variables should be assessed for conformity to linear gradient. Not necessary for dichotomous variables however, dichotomisation of continuous variables not recommended as impacts on statistical power of study.<br>Correlation (test for collinearity) between risk variables should be examined and reported. | Unclear how key variables e.g. liver disease, were defined. To replicate, study investigators would be required to apply own definition which may impact on reproducibility.[112] |

Table 3.2 cont. Criteria to consider when evaluating the quality of risk prediction models

| **Standard criteria[a]** | **Explanation** | **Example** |
|---|---|---|
| Outcome | Method of measuring outcome: must be reproducible and, where assessment scales are applied these should be validated to increase accuracy and reproducibility of the measurement. Dichotomisation of continuous outcomes is not recommended as it can affect statistical power. | Investigators generated own causality assessment of unknown validity.[88]<br><br>Applied widely used, validated causality assessment (Naranjo algorithm).[112] |
| Statistical power | Sample size is calculated based on number of outcome events per variable, where ten events per variable is often recommended. A high number of variables and a rare outcome can result in over-fitting of model, causing poor generalisability. | Reported 86 ADRs in a sample of 690 patients and assessed 34 candidate predictor variables resulting in only 2.5 events per variable.[85] |
| Selection of variables | Independent variable selection should be described clearly and can be based on the literature and/or statistical association as determined by univariate analysis with outcome variable. Selection based upon univariate analysis alone increases likelihood of developing an over-fitted model. Inclusion of variables applicable to over 5% of population may help exclude artefact variables.<br><br>Fitting procedure (entering of variables into model) should be explicitly stated, including removal criteria. | Variables were entered into multivariate analysis if $p<0.05$ after univariate analysis or $p<0.25$ for variables identified from other studies. Liver disease was removed as applied to <5% of population. Backward elimination and forward selection were used with a removal criteria of $p=0.10$.[85] |

Table 3.2 cont. Criteria to consider when evaluating the quality of risk prediction models

| **Standard criteria[a]** | **Explanation** | **Example** |
|---|---|---|
| Model performance | In both development and validation phases, assessment of discrimination and calibration should be reported to determine how well the model distinguishes those who have an ADR from those who have not and how close the prediction is to the observed outcome for that risk group.<br><br>AUROC >0.7 is often deemed acceptable, but this alone is not sufficient to determine the clinical usefulness of the model.<br><br>Assessment of the generalisability of the model is important to determine the accuracy of predictions in another population and is recommended prior to routine clinical application. Internal validation, by methods such as bootstrapping (data resampling) or split-sample, assesses how well predictors correspond to the outcome but lead to optimistic estimates of model performance. External validation is more rigorous and enables assessment of accuracy when the model is applied by investigators not involved in the development of the model. | Discrimination (AUROC[1]) and calibration (Hosmer-Lemeshow) reported in the development and validation phases.[85]<br><br>Trivalle applied bootstrapping.[88]<br><br>Onder applied external validation whereby the model was applied by investigators not in involved in the development of the model and in a different geographical location.[112] |

ADR: adverse drug reaction; AUROC: area under receiver operator curve

[a]Criteria derived from the published literature.[107–110]

[1] Area under the receiver operator curve (AUROC) is a measure of how accurately a model can separate those with and without the outcome of interest i.e. discrimination. An area equal to 1 demonstrates perfect discrimination, an area equal to 0.5 demonstrates that the model is unable to discriminate.

## 3.2 Aim

To undertake a systematic review to identify, and assess the quality of, validated medication risk prediction models to determine their potential benefit to the care of older people.

## 3.3 Objectives

1. To design and apply a search strategy to relevant healthcare literature databases to identify existing validated medication risk prediction models
2. To systematically exclude papers which fail to meet the inclusion criteria
3. To measure the quality of study design and reporting against standard assessment guidelines
4. To identify the most statistically robust model(s) for use in routine clinical practice
5. To identify variables for potential inclusion in future risk prediction models.

## 3.4 Method

### 3.4.1 Information sources and search strategy

A systematic search for published material was performed, using a cut-off of 30th November 2012. Standard databases (Embase, Medline, Cochrane Library, British Nursing Index (BNI), CINAHL, National Electronic Library for Medicines (NeLM), IPA) were searched to identify relevant studies as well as those associated with policy documents and unpublished work (Department of Health, King's Fund, Worldcat, Open Grey, Google Scholar). In addition, for the key studies identified, the bibliographies and citations were reviewed, along with an author search, to identify any additional published studies. The search strategy was verified by two independent information specialists from the Regional Medicines Information Centre, Guy's and St. Thomas' NHS Foundation Trust (GSTFT).

Search strategies were developed for each database in line with their specific requirements and used standard terms based around three key concepts, namely; older people, medication-related problems and clinical prediction models. The full Embase search strategy is outlined. There were no restrictions placed on the search regarding language or date.

### 3.4.2 Embase search strategy

Risk Tool

1. risk assessment.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2. exp prediction/
3. exp scoring system/
4. exp clinical assessment tool/
5. exp risk factor/
6. exp risk management/
7. exp decision support system/
8. risk stratification.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8

Medication related problem

10. exp adverse drug reaction/
11. adverse drug event*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
12. adverse drug reaction*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
13. medication related problem*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
14. drug related problem*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
15. exp medication therapy management/
16. drug/ae [Adverse Drug Reaction]
17. exp polypharmacy/
18. exp medication error/ae, pc [Adverse Drug Reaction, Prevention]
19. inappropriate prescri*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
20. (readmission and drugs).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
21. patient compliance.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
22. 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21

Elderly

23. aged/
24. exp aging/
25. exp elderly care/
26. older people.mp.
27. older person.mp.
28. aged over 80.mp.
29. 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29

Combined terms

30. 9 AND 22 AND 29

### 3.4.3 Inclusion criteria and selection

Two researchers (the principal researcher and a Medicines Information Specialist) independently screened titles and abstracts and, where necessary, full texts to identify those that potentially satisfied the following inclusion criteria:

- Included a majority of patients over the age of 65 years
- Patients who experienced an adverse drug event (ADE) or adverse drug reaction (ADR) but excluding medication errors
- The risk prediction model followed a multivariable approach in design and analysis
- The model had been validated, either internally or externally

### 3.4.4 Search update

The original search was performed on 30th November 2012. To ensure the inclusion of more recent publications in this review, an update search was conducted on 27th October 2016. Given the large number of titles identified through an unavoidably broad initial search strategy, a pragmatic approach was taken for the update search whereby titles and abstracts of papers citing any of the four studies included in the systematic review were assessed against the original inclusion criteria. The development of a new model should consider any existing models in that field[113], and so this method should allow identification of any models published in this area since the original search.

### 3.4.5 Data Extraction

Data were extracted to provide detail of the population characteristics, study design, process of model development and validation, and performance of the model as presented in Table 3.4 and Table 3.5. This was confirmed by a Medicines Information Specialist, GSTFT, and a statistical expert, King's College London (KCL), and any disagreement resolved through discussion.

### 3.4.6 Quality assessment

All papers were initially reviewed using a "gold standard" approach for developing and testing clinical prediction models to satisfy a range of criteria representing 4 stages: development

(identification of candidate predictor variables and model design), validation (testing the performance of the model), impact (measurement of usefulness in the clinical setting) and implementation (widespread acceptance and adoption in clinical practice).[91]

As no standardised quality assessment for risk prediction models was available at the time, each study was analysed using criteria derived from the published literature[107–110] as outlined in Table 3.2. Candidate predictor variables were grouped into 3 categories to allow comparison between studies; social factors (e.g. function), medical factors (e.g. co-morbidities) and medication factors (e.g. class of medicine). The event rate was calculated as a percentage ADR/ADE rate where it was not reported by the authors in this form. The overall performance of the models was determined by a review of their accuracy, discrimination and calibration.

## 3.5 Results

A total of 13423 titles were identified from the literature as potentially relevant, of which only 549 were associated with adverse outcomes of medicines use. The majority of these (535) were excluded on review of the abstract, as they were not associated with the design of a risk prediction model, many being observational in nature (Figure 3.1). Full papers were requested for the remaining 14 articles for further scrutiny against the inclusion criteria and four met the inclusion criteria and were subjected to a full evaluation.[85,88,89,112]

The update search generated one title satisfying the inclusion criteria which had already been identified in the original search of the grey literature. This publication[19] uses the data from Tangiisuran's thesis[85] and upon evaluation, this recent publication provided no additional information to that already obtained from the thesis.

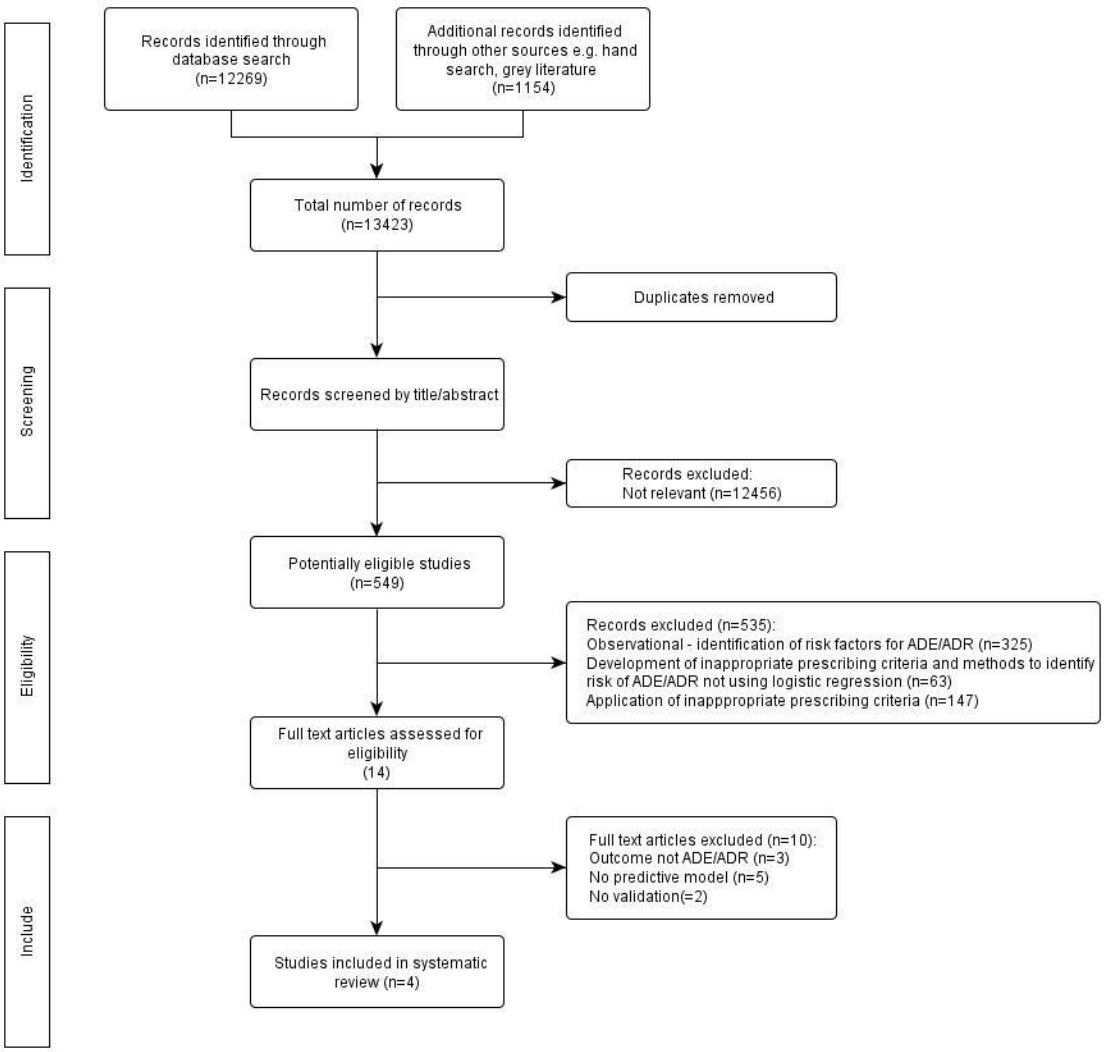



Figure 3.1 PRISMA flow diagram describing paper inclusion for systematic review (original search date 30th November 2012)

### 3.5.1 Excluded papers

Although the 535 articles excluded were associated with describing the adverse outcomes of medicines, none went on to design a risk prediction model. These articles could be further categorised into three sub-groups. The first sub-group (325 studies) involved observational studies reporting the incidence of, and factors associated with, ADRs or ADEs. In some instances, these described the patient population associated with the four studies which met the inclusion criteria.[114,115] The second sub-group (63 studies) included those where quality prescribing indicators had been developed. These were usually in the form of a list of potentially inappropriate medicines often associated with common conditions seen in older people, for example Beers' criteria[57,116–118], STOPP/START criteria[119], and the MAI[83]. The final sub-group

(147 studies) was where the prescribing indicators were applied within a clinical setting to determine any association between the prescribing of inappropriate medicines and adverse outcomes.

### 3.5.2 Included papers

All four studies included in the systematic were conducted in Western Europe over the past twenty years with the intention of identifying older inpatients at risk of ADRs (Table 3.3). Two studies[85,112] assigned names to their models.

Table 3.3 Summary of included studies

| Author | Publication Date | Country of origin | Setting for use | Model name |
|---|---|---|---|---|
| McElnay[89] | 1997 | UK | Inpatient | None given |
| Tangiisuran[85] | 2009 | UK | Inpatient | Brighton ADR Risk (BADRI) model |
| Onder[112] | 2010 | Italy | Inpatient | GerontoNet ADR risk score |
| Trivalle[88] | 2011 | France | Inpatient | None given |

#### 3.5.2.1 Population characteristics

The population characteristics of the studies included in the systematic review are summarised in Table 3.4. The development phase datasets were generated across a range of care settings (acute, community and rehabilitation hospitals). Two of the four studies represented the oldest old (aged over 80 years).[85,88] Only one study, Tangiisuran, reported on the ethnic profile of the study population.[85]

Comorbidities, where reported, were dominated by diseases of the cardiovascular system, including hypertension, cerebrovascular disease and coronary heart disease. Also included were diabetes, COPD, musculoskeletal, gastrointestinal, genitourinary and neurological conditions. The mean number of drugs prescribed (range 4.3-9.4 per patient) increased as publication date became more recent. Medical and medication factors were considered in all studies. Social or patient factors, e.g. patient functionality, were reported by Onder[112], Tangiisuran[85] and McElnay[89] and were measured using different methods. Examples of these factors include: Onder[112] and Tangiisuran[85] captured activities of daily living using the Katz Index[120] and Barthel Index[121]

respectively; McElnay[89] explored "healthcare behavioural factors" including whether the patient thought that the drug was responsible for the admission to hospital.

The primary outcome in all of the studies was ADR, based on the WHO definition, "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[8] One study used ADE synonymously[88] and another included ineffective treatment, for example due to non-compliance, in an extended definition[89]. The proportion of patients who experienced an ADR/ADE ranged from 6.5% - 39%, with gastrointestinal, cardiovascular, and nervous systems the most frequently affected. This range is likely to be reflective of variation in the study design. It would be expected that a broader definition of ADR, such as that used by Trivalle[88], would produce a larger rate of events (39%). Conversely, a more focussed definition, as used by Tangiisuran[85] and Onder[112], would produce a lower rate of events (12.5% and 6.5% respectively). Furthermore, the retrospective study design applied by Onder and colleagues may explain the comparatively low outcome rate reported.[112] A systematic review of the prevalence of ADRs in older patients in the acute setting found the prevalence of ADRs to be lower in studies with a retrospective design.[122] Medications most frequently associated with ADRs/ADEs included psychotropics, anticoagulants and analgesics. The risks associated with the use of psychotropic and anticoagulant medications in older adults is well documented.[123,124] Analgesics, as described by Tangiisuran, included both opioid and non-steroidal anti-inflammatory drugs (NSAIDs), whereas Trivalle did not include (NSAIDs). Nevertheless, both groups of drugs are commonly identified as being potentially problematic in older adults due to side effects such as sedation and constipation in the case of opioids[125] and gastrointestinal, renal and cardiovascular adverse events with NSAIDs.[126]

Table 3.4 Summary of population characteristics of included studies

| Author | Development | | | | | | Validation |
|---|---|---|---|---|---|---|---|
| | **Population and setting** | **No. of patients (n), co-morbidities (%)** | **No. of drugs** | **Outcome (rate) (%)** | **Drug associated with primary outcome (%)** | **Systems affected by ADR (%)** | **Population and setting** |
| McElnay[89] | Age: 65-98 years<br>Location: Acute hospital (UK)<br>Year: NR (published in 1997)<br>Gender: F 50%,<br>Ethnicity: NR | n = 929<br>Co-morbidities not reported | Mean: 4.3<br>Range: 1-15, SD: NR | ADE (16)<br>- ADR and adherence | Digoxin (NR)<br>ACE inhibitors (NR)<br>Antidepressants (NR)<br>Insulin (NR) | NR | n = 204 (number ADRs unknown)<br>Cohort similar to development cohort |
| Tangiisuran[85] | Age: 85±7.9 years<br>Location: Acute hospital (UK)<br>Year: 2007 & 2008<br>Gender: F 61%,<br>Ethnicity: White | n = 690<br>HTN (73)<br>Infection (44)<br>Anaemia (41)<br>MSK (41) | Mean: 7<br>Range: 5-10, SD: NR | ADR (12.5) | Cardiovascular (34)<br>Analgesics (16)<br>Antidiabetics (13)<br>Antibiotics (13) | GI (21.1%), CV (20)<br>Neuropsychiatric (14.7)<br>Endocrine (13.7)<br>Metabolic/renal (11.6) | n = 483 (56 suffered ADR)<br>Number of drugs 11.0±7.0<br>Cohort similar - from 4 European countries (UK, Belgium, Italy and Netherlands) |

Table 3.4 cont. Summary of patient population characteristics of included studies

| Author | Development | | | | | | Validation |
|---|---|---|---|---|---|---|---|
| | **Population and setting** | **No. of patients (n), co-morbidities (%)** | **No. of drugs** | **Outcome (rate) (%)** | **Drug associated with primary outcome (%)** | **Systems affected by ADR (%)** | **Population and setting** |
| Onder[112] | Age: 78±7.2 years<br>Location: Acute and community hospitals (Italy)<br>Year: 1993-1997 | n = 5936<br>HTN (24)[a]<br>CHD (21)[a]<br>Diabetes (16)[a]<br>COPD (14)[a]<br>Cerebrovascular disease (13)[a] | Mean: 6.3<br>Range: NR, SD 3.6 | ADR (6.5) | Antineoplastics (19.5)[a]<br>NSAIDs (5.2)[a]<br>Antipsychotics (4.4)[a]<br>Antibiotics (3.9)[a]<br>Corticosteroids (3.3)[a] | GI (18)<br>CV (25.3)<br>Neuropsychiatric (17.8)<br>Dermatologic (11.7) | n = 483 (56 suffered ADR)<br>Number of drugs 11.0±7.0<br>Cohort similar - from 4 European countries (UK, Belgium, Italy and Netherlands).<br>*Secondary Study*[60]<br>n = 513 (135 ADRs)<br>Number of drugs 7 (IQR 7-10)<br>Cohort similar - from Rep. of Ireland. |

Table 3.4 cont. Summary of patient population characteristics of included studies

| Author | Development | | | | | | Validation |
|---|---|---|---|---|---|---|---|
| | **Population and setting** | **No. of patients (n), co-morbidities (%)** | **No. of drugs** | **Outcome (rate) (%)** | **Drug associated with primary outcome (%)** | **Systems affected by ADR (%)** | **Population and setting** |
| Trivalle[88] | Age: 83.6±7.9 years<br>Location: 16 rehabilitation hospitals (France)<br>Year: NR<br>Gender: F 72%, Ethnicity: NR | n = 576<br>CV (72), MSK (48), GI (36),<br>GU (29)<br>Neuro (26) | Mean: 9.4<br>(Range: NR)<br>(SD 4.24) | ADE (39) (not all were included) | Psychotropics (23)<br>Antihypertensives (17)<br>Anticoagulants (14)<br>Analgesics (13) | GI (25)<br>Biological abnormalities (22)<br>Other (20)<br>Neuropsychiatric (12) | Bootstrapping<br>n = NR<br>Validation cohort similar to developmental cohort |

ACE: Angiotensin Converting Enzyme; ADE: Adverse Drug Event; ADR: Adverse Drug Reaction; CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease; CV: Cardiovascular; F: female; GI: Gastrointestinal; GU: Genitourinary; HTN: Hypertension; MSK: Musculoskeletal; NR: Not recorded; NSAIDs: Non-Steroidal Anti-Inflammatory drugs; SD: Standard Deviation;

[a]Data extracted from the Gruppo Italiano di Farmacoepidemiologis nell Anziano (GIFA) study[114]

#### 3.5.2.2 Quality assessment

None of the four models meeting the inclusion criteria satisfied all four key stages in the creation of a quality risk prediction model. Whilst all models included the development and validation phases, none addressed the impact and implementation phases, although it is possible that this work may be in progress and the findings have not, as yet, been published. However, given the time elapsed since development of the model and personal communication with Tangiisuran and Onder, it would seem unlikely that the impact and implementation of the models, in their current form, will be conducted.

#### 3.5.2.3 Model development

##### 3.5.2.3.1 Study design

For participant sampling in the development phase all, except Onder[112], used a prospective case-cohort design method, where events accrued over the study period (Table 3.5). Onder and colleagues[112] drew their data from a previously established historical database. Data were extracted over a 3-year period in this study in comparison to the studies with a prospective design, where data extraction varied between one and six months, depending on study design. Prospective study design is beneficial as it allows optimal collection of potential candidate variables; this is because standardised measurements of variables can be applied and the likelihood of missing data can be minimised. The use of a retrospective dataset does not allow for this level of detail and relies upon data collected previously, often for another reason. Consequently, it is not possible to extract or confirm some aspects of the data resulting in uncertainty with regards to definitions of variables and the reason for any missing data. Patient medical notes, in-patient charts and electronic records were reviewed in the prospective studies.[85,88,89] In addition, McElnay[89] asked patients directly about aspects of their medicines while Trivalle[88] used patient self-reporting of any medication-related problems as a trigger for further analysis. The validation phase was conducted prospectively for all studies except Trivalle[88], where bootstrapping, a re-sampling technique[109], was used.

Table 3.5 Summary of quality assessment of included studies

| **Standard criteria** | | **McElnay**[89] | **Tangiisuran**[85] | **Onder**[112] | **Trivalle**[88] |
|---|---|---|---|---|---|
| **Study design** | | Prospective cohort (development and validation) | Prospective cohort (development and validation) | Retrospective cohort (development)<br>Prospective (validation) | Prospective cohort (development)<br>Retrospective cohort (validation) |
| **Participant recruitment** | **Clear inclusion criteria** | Yes<br>Development<br>- Non-elective admissions to medical, surgical, cardiac and geriatric wards in a single hospital<br>- > 65 years old and taking medicines<br>Validation<br>- as above | Yes<br>Development<br>- Non-elective admission to Care of the Elderly wards in a teaching hospital<br>- > 80 years old<br>Validation<br>- admitted to 1 of 4 European hospitals<br>- ≥ 65 years old and taking medicines | Yes<br>Development<br>- Community and teaching hospital admissions<br>- ≥ 65 years old and taking medicines<br>Validation<br>- as above except admitted to 1 of 4 European hospitals | Yes<br>Development<br>- Consecutive admissions to 16 geriatric rehabilitation centres<br>Validation<br>- as above |
| | **Evidence patient selection was not biased** | Unsure<br>Data only collected from patients recruited who underwent interview (50% development, 42% validation) | Yes<br>All patients excluded were for appropriate reasons | Unsure<br>An unknown number of patients were excluded due to incomplete data<br>61 cancer patients excluded | Unsure<br>Data from 71 patients were excluded (either were part of an intervention arm or were not present for study duration) |
| | **Acceptably low loss to follow up** | Yes<br>Data from all interviewed patients were used | Yes<br>No patients lost to follow up | Yes<br>No patients lost to follow up | Yes<br>No patients lost to follow up |

Table 3.5 cont. Summary of quality assessment of included studies

| Standard criteria | | McElnay[89] | Tangiisuran[85] | Onder[112] | Trivalle[88] |
|---|---|---|---|---|---|
| Candidate predictors variables[a] | **Clear methods used to measure predictors** | Partly<br>2 of 7 identified variables were not easily quantifiable (GI problems, patient thinks drugs responsible for hospital admission) | Partly<br>Data on 17 potential variables assessed. Not clear how co-morbidity, liver disease, previous history of ADR or known allergy to medication were defined | Partly<br>Trained physicians completed questionnaires but unclear how variables were defined (comorbidities, liver disease, ADR history) or consistently applied | Partly<br>Where candidate predictors were reported they could be clearly described. Potential candidate predictors which were not included in the model are unknown. |
| | **Blinding to outcome** | Yes<br>Data collected prospectively | Yes<br>Data collected prospectively | Partly<br>Blinding is not reported for the development phase. Physicians collecting data for the validation phase were blinded. | Yes<br>Data collected prospectively |
| | **Conformity with linear gradient** | Not reported | Not reported | Not reported | Yes<br>Linearity was checked where possible |
| | **Test for collinearity** | Partly<br>Outlined in method but not mentioned in results. | Partly<br>Outlined in method but not mentioned in results. | Not reported | Yes<br>High correlation risk factors were identified and examined in separate models. |

Table 3.5 cont. Summary of quality assessment of included studies

| Standard criteria | | McElnay[89] | Tangiisuran[85] | Onder[112] | Trivalle[88] |
|---|---|---|---|---|---|
| **Outcome**[b] | **Appropriate methods used to measure outcomes** | Partly<br>Data from patient records and interviews<br>ADE as defined by:<br>- ADR (measured using modified Naranjo scale)<br>- Adherence (self-report) | Partly<br>Medical information and healthcare staff reviewed daily using standardised checklist. Suspected ADRs assessed for causality, preventability and severity using Naranjo algorithm, Hallas criteria and a confidence in causality likert scale. | Partly<br>Wards visited daily and nursing and medical records examined daily. Causality was assessed based on Naranjo algorithm. | Partly<br>A combination of approaches used to identify ADEs: self-generated standardised 32 item checklist was completed by nursing staff, incident reporting and weekly chart review. Four criteria were used to assign likelihood of causality. |
| **Statistical power** | **Sufficient EPV (i.e. >10)** | No<br>Unable to determine exact number but <10. | No<br>86 ADRs/34 candidate predictor variables = 2.5 | Yes<br>Unable to determine exact number but >10. | Unsure<br>Not possible to determine |
| **Selection of predictor variables** | **Method of selection reported for independent variables** | Partly<br>Screened in univariate analysis and entered into model if p<0.25. Applicable to >5% of population. | Yes<br>Screened in univariate analysis and entered into model if p<0.05. Variables identified from other studies entered into model if p<0.25.<br>Applicable to >5% of population. | Yes<br>Screened in univariate analysis and entered into model if p≤0.10. | Yes<br>Screened in univariate analysis and entered into model if p<0.05. Applicable to >5% of population. |

Table 3.5 cont. Summary of quality assessment of included studies

| Standard criteria | | McElnay[89] | Tangiisuran[85] | Onder[112] | Trivalle[88] |
|---|---|---|---|---|---|
| **Selection of predictor variables** | **Fitting procedure reported** | Yes<br>Stepwise backward elimination procedures (using maximum likelihood method).<br>Preliminary removal of variables at p=0.15 then p=0.05. | Yes<br>Multivariate logistic regression - using backward elimination procedure and forward selection.<br>Removal criteria p = 0.10. | Partly<br>Stepwise logistic regression.<br>Added and retained variables if p≤0.1.<br>Method elimination and retention unclear. | Partly<br>Stepwise logistic regression.<br>Retained variables if p<0.05.<br>Method elimination and retention unclear. |
| **Model performance** | **Development phase reported** | No | Yes<br>Discrimination as AUROC reported with CI<br>Calibration as Hosmer-Lemeshow and Nagelkerke R2<br>Sensitivity and specificity reported. | Partly<br>Discrimination as AUROC reported with CI<br>Sensitivity and specificity reported | No |

ADE: Adverse Drug Event; ADR: Adverse Drug Reaction; AUROC: Area Under Receiver Operator Curve; CI: Confidence Interval; EPV: events per variable; GI: Gastrointestinal

#### 3.5.2.3.2 Participant recruitment

Recruitment of participants, the criteria for inclusion and exclusion and any loss to follow up were clearly described in all studies but reporting of patient selection was poor. Data were only collected through interview for 50% and 42% of patients in the development and validation phases respectively in the study by McElnay.[89] Patients who were not interviewed either refused, or had already been discharged, or were too ill.[89] Trivalle[88] excluded patients who were not present for the study duration or were recruited to the intervention arm of another linked study. Twenty seven percent of the study population were excluded in the study by Tangiisuran[85]: 111 (43%) were under 65 years old and; 145 (57%) either died, the medical notes were unavailable or they were discharged within 24 hours of admission or during the weekend. An unknown number of patients were excluded from Onder[112] due to incomplete data. It is extensively reported that missing data rarely occurs completely at random and exclusion of participants with incomplete data can affect statistical power and introduce bias[109] e.g. the relationship between the candidate predictor variables and the outcome is different between participants with complete and incomplete data.

#### 3.5.2.3.3 Candidate predictors variables

Candidate predictor variables (the risk factors being investigated in the study) were, in general, handled poorly. In all studies the description of the variables was inadequate; where Trivalle[88] did not report the potential candidate variables, McElnay[89], Tangiisuran[85] and Onder[112] used variables with unclear definitions, e.g. previous ADR. Despite being labelled as a "bad idea"[127], dichotomisation of continuous candidate predictor variables (e.g. ≥4 comorbidities, >8 medications, previous ADR) was common practice, and may explain the failure to consider conformity with the linear gradient in all but the Trivalle study[88]. Interactions between independent variables, that is where one independent variable's relationship with the outcome is changed by the presence of another independent variable, should be considered when developing a risk prediction model. Where significant interactions exist there may be overfitting of the model and ultimately poor generalisability.[128] Interactions were poorly addressed in all studies. Insufficient detail in the results made it difficult to establish if tests mentioned in the methods had been implemented, e.g. McElnay[89] reported testing for interactions and collinearity but this was not followed through to the results. Predictor variable measurement was blinded for outcome in the

development phase of three[85,88,89] of the four studies given the nature of their prospective design. Onder[112] did not mention blinding.

#### 3.5.2.3.4 Outcome

The occurrence of an ADE/ADR was the primary outcome measure for all studies. Each study used different procedures to identify, categorise and confirm the primary outcome. Tangiisuran, who was the primary researcher (a pharmacist), identified cases and discussed all suspected ADRs with the attending hospital physician. These were then confirmed by a physician, independent of the study. All ADR cases, and 45 non-ADR cases were then reviewed, categorised and confirmed by another independent reviewer and agreement with the primary researcher on classification reached through discussion.[85] Trivalle followed a similar method whereby nurses (alongside the study investigators) initially identified potential ADEs which were subsequently reviewed on a monthly basis by a team of pharmacists and physicians. It is unclear if this group was independent of the study. Finally, a select group of reviewers (from the research team) reviewed and classified all medicines related incidents.[88] Onder only reported that the initial identification of an ADR was conducted by the study physician[112] and McElnay did not report any part of the procedure used for identification, categorisation or confirmation of ADRs[89]. A multiple step approach to determining the occurrence of ADEs/ADRs is important to ensure validity and reliability of the results. In addition, a validated assessment of causality, in the form of the Naranjo algorithm[129] or Hallas criteria[130], was adopted by all but Trivalle[88], who developed their own unvalidated checklist. The outcome was recorded in the form of continuous categorical data, i.e. unlikely, possible, probable, definite, which was then collapsed to produce a binary outcome. For example, Tangiisuran[85] combined possible, probable and definite as a positive outcome, i.e. the participant had suffered an ADR. Such an approach can affect the statistical power of the research[109] however, it may be necessary due to a small number of events or when it is difficult to categorically state that the event was due to a specific medicine. The latter often being the case when investigating harm due to medicines in an older population who may present with atypical signs and symptoms and are frequently multimorbid and taking many medicines.

Blinding to the outcome occurred in all four studies during the validation phase due to the prospective nature (three studies)[85,89,112] and the use of bootstrapping, computer simulated re-sampling technique (one study)[88].

#### 3.5.2.3.5 Statistical power

The poor description of potential candidate predictor variables makes it impossible to determine if the studies were adequately powered. It is commonly understood that study sample size is based on the number of outcome events per variable, where ten events per variable is often recommended (however sometimes a lower rate may be appropriate).[96–98,131] That is, for every candidate predictor variable considered in a development study, not just those considered or included for multivariable analysis, there should be 10 events. Van Smeaden and colleagues recently called into question this rule and describe the evidence to support its use as "weak".[132] It is worth noting however, that a high number of variables and a rare outcome can result in over-fitting of the model (Type I error), thus reducing reliability and reproducibility, leading to poor generalisability. Under-fitting (Type II error) where important variables are omitted and paradoxical fitting (Type III error) where variables are given an "incorrect direction of association" can also result from an inadequate event per variable ratio.[97] Trivalle[88] did not report the candidate predictor variables and, Tangiisuran[85] and McElnay[89] failed to reach the recommended 10 events per variables. Onder[112] had approximately 17 events per variable.

#### 3.5.2.3.6 Selection of predictor variables

The method of selecting predictor variables for inclusion within the multivariable analysis, also known as the fitting procedure or model selection, was described in all four studies (Table 3.5). Tangiisuran[85] provided the most detailed description of the methods used to select candidate predictor variables, whilst Trivalle[88] provided the least. Although there is no standardised method for selecting candidate predictor variables for multivariate analysis, it is recognised that selection through univariate analysis alone may result in an over-fitted model with spurious predictions. Mixed methods, for example using the literature or expert opinion, and univariate analysis, are recommended for variable selection as demonstrated by Tangiisuran.[85] Inclusion of candidate predictors prevalent in at least 5% of the population can also improve the applicability of the final

model.[85,88,89] In addition there is no set significance level for retaining a variable in the model and so it can vary, for example Onder[112] set p≥0.1, McElnay[89] set p<0.25. A set statistical significance is used in variable selection merely as an objective variable selection method. Furthermore, when selecting variables it is important to consider cost, accessibility in relation to additive predictive value and clinical relevance.

#### 3.5.2.4 Model performance and validation

Assessment of the performance of the model allows an understanding of how well the predictions from the model match the observed values. Two common forms of performance assessment are discrimination and calibration, where discrimination is the ability to separate those with, or without, the outcome of interest while calibration is the agreement between the predicted outcome and the observed outcome. The AUROC is commonly reported for discrimination where a value of >0.7 may be deemed acceptable, but this alone is not sufficient to determine the clinical usefulness of the model.[109] AUROC was reported by three of the four studies with values ranging between 0.70-0.74 for the development phase (see Table 3.6), which involves estimating model values in an initial dataset. Calibration is assessed using two statistical tests, Hosmer-Lemeshow test[133] and Nagelkerke R2[134]. Calibration was only reported by Tangiisuran; for which Hosmer-Lemeshow was satisfactory but Nagelkerke was low which is suggestive of a small effect size.[85] Sensitivity and specificity were reported by Tangiisuran[85], Onder[112] and McElnay[89] (see Table 3.6). Tangiisuran[85] reported the highest sensitivity (80%)[858483], in comparison to Onder[112] reporting 68% and McElnay[89] 40.5%. With regards to specificity, Onder[112] reported the highest (65%), with McElnay[89] reporting 69% and Tangiisruan[85] 55%.

All models underwent the subsequent stage of validation using a second dataset of patients, which should be conducted prior to the application of a model in the clinical setting.[93] Internal validation was reported by McElnay[89] and Trivalle[88] in the form of two approaches: 'split sample' (separate evaluation in a second dataset) and 'bootstrapping' (sampling within a dataset). Whilst the latter can be useful in testing how well the predictors correspond to the outcome in the development population, it fails to assess the generalisability of the model. Good generalisability is important if a model is to be of benefit outside of the population in which it was derived. Internal validation, in the same sample, tends to lead to optimistic estimates of a model's performance,

due to the ignoring of sample to sample variation. External validation is the most rigorous form of validation and was performed by both Onder[112] and Tangiisuran[85], in the same multi-site European prospective cohort. In addition, a research group from Ireland[60] subsequently applied the model developed by Onder[112] in their local population, providing additional external validation. The characteristics of the validation populations are described in detail in Table 3.4. The number of patients involved in the external validation ranged from 204 to 483. AUROC in the validation phase ranged from 0.62-0.73.

#### 3.5.2.5 Score development

Predictor variables within the final models (Table 3.6) were attributed a points-based score, using different methods in three of the four models, as a simplification for practical application. McElnay and colleagues[89] did not proceed to this stage due to the poor performance of their model. The methods used by Onder[112] and Tangiisuran[85] are outlined, with Tangiisuran arguably using the more robust approach to score development. The score developed by Onder[112] was on a points-based system where a predictor variable with an OR in the range 1.00-1.99 was assigned 1 point for individuals with that predictor present; for predictors with OR in the range 2.00-2.99, 2 points; predictors with OR 3.00-3.99, 3 points; and for predictors with OR in the range 4.00-4.99, 4 points. There was no assessment to determine if any of the predictive ability was lost in this simplification. Tangiisuran[85] assigned one point to each predictor variable based on the variable coefficient being of the same magnitude. It is unclear how Trivalle[88] assigned the values to each predictor variable.

Table 3.6 Summary of final ADR prediction models and scoring

| Author | Significant variables (multivariate analysis) | Variable coefficient | OR (95% CI) | Score | Validation |
|---|---|---|---|---|---|
| **McElnay**[89] | Prescribed antidepressants | 1.76 | 5.79 (2.12-15.85) | None | Internal (n=204) |
| | Prescribed digoxin | 0.69 | 1.99 (1.05-2.33) | | Accuracy 63% |
| | Gastrointestinal problems | 0.77 | 2.16 (1.13-4.15) | | Sensitivity 40.5% |
| | Abnormal potassium | 0.95 | 2.57 (1.35-4.91) | | Specificity 69.0% |
| | Thinks drugs responsible | 1.44 | 4.21 (2.18-8.14) | | |
| | Experiences angina | -1.79 | 0.16 (0.07-0.42) | | |
| | Experiences COAD | 0.88 | 2.41 (1.06-5.44) | | |
| | | -1.10 (constant) | | | |
| **Tangiisuran**[85] | Hyperlipidaemia | 1.20 | 3.32 (1.81-6.07) | 1 | External (n=483) |
| | Number of drugs ≥8 | 1.20 | 3.30 (1.93-5.65) | 1 | Sensitivity 80.0% |
| | Length of stay ≥12 days | 0.82 | 2.27 (1.35-3.83) | 1 | Specificity 55.0% |
| | Hypoglycaemic agents | 0.65 | 1.91 (1.04-3.49) | 1 | AUROC 0.73 (95% CI 0.66-0.80) |
| | High admission WBC count | 0.44 | 1.55 (0.94-2.55) | 1 | |
| | | -3.63 (constant) | | 1 | |

Table 3.6 cont. Summary of final ADR prediction models and scoring

| Author | Significant variables (multivariate analysis) | Variable coefficient | OR (95% CI) | Score | Validation |
|---|---|---|---|---|---|
| **Onder**[112] | ≥4 comorbidities | NR | 1.31 (1.04-1.64) | 1 | *Onder* [112] |
| | Heart failure | | 1.79 (1.39-2.30) | 1 | External (n=483) |
| | Liver disease | | 1.36 (1.06-1.74) | 1 | Sensitivity 68% |
| | Number of drugs <5 | | 1 Reference | - | Specificity 65% |
| | Number of drugs 5-7 | | 1.90 (1.35-2.68) | 1 | AUROC 0.70 (95% CI 0.63-0.78) |
| | Number of drugs ≥8 | | 4.07 (2.93-5.65) | 4 | *O'Connor* [60] |
| | Previous ADR | | 2.41 (1.79-3.23) | 2 | External (n=513) |
| | Renal failure (eGFR <60ml/min) | | 1.21 (0.96-1.51) | 1 | AUROC 0.623 (95% CI 0.570-0.676) |
| **Trivalle**[88] | Number of drugs | NR | 1.90 (1.60-2.30) | - | Internal (bootstrap) |
| | 0-6 | | | 0 | AUROC 0.70 (95% CI 0.65-0.74) |
| | 7-9 | | | 6 | |
| | 10-12 | | | 12 | |
| | ≥13 | | | 18 | |
| | Antipsychotic treatment | | 2.50 (1.50-4.10) | 9 | |
| | Recent anticoagulant | | 2.00 (1.10-1.37) | 7 | |

ADR: Adverse Drug Reaction; AUROC: Area Under Receiver Operator Curve; CI: Confidence Interval; COAD: Chronic Obstructive Airways Disease; eGFR: estimated glomerular filtration rate; OR: Odds ratio; WBC: White Blood Cell; NR: Not Reported

#### 3.5.2.6 Impact and implementation

The impact and implementation of these models have not, as yet, been assessed - perhaps due to their poor to modest performance. McElnay[89] recognised the limitation of the level of performance and both Tangiisuran[85] and Onder[112] call for further external validation of their risk models. However, Trivalle[88] concluded that their Geriatric Risk Score could be applied in clinical practice alongside other prognostic and diagnostic tools such as the Mini Mental State Exam.

The challenges of using unclear definitions with certain variables as highlighted by O'Connor[60] in the application of Onder's risk model should be heeded as similar difficulties are likely to arise when applying Tangiisuran[85], Trivalle[88] and McElnay[89] given the poorly defined predictor variables outlined earlier. The use of variables such as length of stay would also make prospective risk stratification, e.g. at the point of admission, impossible.

## 3.6 Discussion

This review suggests that the four models identified, which were designed to predict the risk of older patients suffering an adverse drug reaction, are not yet suitable for use in routine clinical practice. While two (Tangiisuran[85] and Onder[112]) had been externally validated, their ability to discriminate between those who had experienced an ADR and those who had not was only modest, AUROC 0.73 and 0.70 respectively. In practice this could result in failure to identify patients at high-risk of experiencing an ADR for more intensive review. Furthermore, none were subjected to the investigational rigour required when producing a risk prediction model, in particular none reported the findings of impact and implementation stages thereby widening the gap between research potential and clinical application.[135]

All four studies had limitations commonly found in this research field. While three of the studies failed to provide sufficient information relating to events per variable ratio[131], one was insufficiently powered[85] so that the risk of a Type II error (false negative finding) is more likely.[136] In addition, all studies dichotomised predictor variables (for example when categorising the number of medicines) and outcomes (for example collapsing an ADR causality interval scale) despite this practice being sub-optimal.[137] This approach to data handling reduces the confidence in the findings due to the risk of Type I errors (false positive findings).[136] The use of unrepresentative samples and the issue of how missing data were managed were also problematic regardless of

the retrospective or prospective design. There was often a lack of reporting of all candidate predictor variables which hinders replication by others, and consequently the assessment of generalisability, and confirmation of genuine predictor variables through external validation.[138,139]

Although research investigating medication risk in older adults is growing, as evidenced by the over 500 titles identified in the initial search, almost all were associated with other approaches to managing risk and a substantial proportion were observational. This poses the question how do we move forward with research in this area? There appear to be two main challenges. Firstly, when conducting literature searches in both risk prediction and ADR studies, a broad search strategy must be adopted to ensure that all studies are identified. Secondly, in order to identify genuine predictor variables consideration must be given to the care setting, the characteristics of the population to be studied (for example frail older adults), clarity of outcome definitions (ADR versus ADE) and the sample size. These challenges have been recognised by the Cochrane Prognosis Methods Group and the Prognosis Research Strategy (PROGRESS) partnership, who have developed a number of recommendations to assist investigators in combating the range of challenges. A Medline search filter has been created to assist in the identification of relevant literature[135,136,140–142] and since this review was conducted reporting guidelines have been developed for authors to apply to their protocols and manuscripts when designing or publishing risk prediction research (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis – TRIPOD - guidelines).[143]

Weaknesses are evident in the models identified however they do make an important contribution to the future development of risk prediction models in this field. Application of these models to large datasets, through close collaboration as illustrated by the pan-European work of Onder and colleagues[113,141] may help identify genuine predictor variables and generate a generalisable inpatient model.

### 3.6.1 Limitations

A limitation of this systematic review is that we could not assess for publication bias using conventional methods such as funnel plots due to the small number of studies available.[144] It should be highlighted however, that publication bias is likely to be present as suggested by the strong body of evidence generated by work in the cancer risk prediction field.[68] Registration of

risk prediction research, as is increasingly being championed for all clinical trials (www.alltrials.net), should go some way to reduce future reporting bias.[141] A further limitation is that, in the absence of a consensus guideline, this systematic review adapted three sets of recognised standards for reporting risk prediction research. The rationale for this approach was to reduce the likelihood of any important quality measures being excluded.

### 3.6.2 Further ADR risk prediction models

After the completion of the updated systematic review (October 2016), Nair and colleagues published the Prediction of Hospitalization due to Adverse Drug Reactions in Elderly Community Dwelling patients (The PADR-EC score).[68] The model was developed to predict the risk of community patients being admitted to hospital due to ADRs. Participants were recruited prospectively upon admission to hospital for acute, unplanned care. It was reported that 39.6% (n=503) of the study population were excluded: 130 (25.8%) were unwilling to consent and 373 (74.2%) were unable to be interviewed. A summary of the population characteristics is provided in Table 3.7. As with the previous studies reviewed, common diseases included those of the cardiovascular system. In contrast, renal failure was the most frequently reported comorbidity, affecting almost half the study population (48.4%). This may be reflective of the point in time that the measurement was conducted and the acute nature of the participant's presentation, in comparison to the participants in the other studies who were inpatients and any acute renal dysfunction may have already been corrected. ADRs, based on the WHO definition[8], were identified using medical records and interviews with the patient or relative. A patient was classified as having an ADR if a known adverse effect of a medication was described, there was a temporal relationship, and other causes could be excluded. Causality was determined using the Naranjo algorithm[129] and preventability using Schumock and Thornton criteria[145]. It was unclear who conducted the initial assessment but all patients who were suspected of having an ADR, and 10% of cases where there was said to be no ADR, were assessed by a clinical pharmacist. The clinical pharmacist and researcher met to reach a consensus. An ADR was reported in 15% of the population, a rate similar to that reported by Tangiisuran[85] and McElnay[89] for inpatient ADR. Medications prescribed for the management of cardiovascular disease were most commonly associated with an admission due to an ADR.

Table 3.7 Summary of population characteristics of Nair and colleagues study

| Development | | | | | Validation |
|---|---|---|---|---|---|
| **Population and setting** | **No. of patients (n), co-morbidities (%)** | **No. of drugs** | **Outcome (rate) (%)** | **Drugs associated with primary outcome (%)** | **Population and setting** |
| Age: 80.1±7.7 years<br>Location: Acute hospital (Australia)<br>Year: 2014-15<br>Gender: F 52.2% Ethnicity: NR | n = 768<br>Renal failure (48.4)<br>Anaemia (39)<br>Vascular disease (36.8)<br>Hyperlipidaemia (28.6)<br>Diabetes (28.1) | Mean: 10.8<br>Range: NR<br>SD: 5.2 | ADR (15) | Antithrombotics (68)<br>ACEIs or ARBs (54.7)<br>1-2 Antihypertensives (50.2)<br>Antiplatelets (49)<br>Diuretics (47.3) | n = 240 (30 suffered ADR)<br>Number of drugs 9.9 ± 4.8<br>Cohort similar to development cohort |

ACEIs: angiotensin converting enzyme inhibitors; ADR: adverse drug reaction; ARBs; angiotensin receptor blockers; F: female; NR: not reported; SD: standard deviation

Nair and colleagues[68] reported on the validation of the model, however they did not proceed to the impact and implementation stages that are recommended in the development of a quality risk prediction model. Similar limitations were identified to those described for the models developed for inpatient use. The recently published TRIPOD guidelines[143] were applied to this study. It was identified that only one third (10/31) of the recommended reporting criteria for the development of a risk prediction were fully met (Table 3.8). The reporting of missing data and the calculation of sample size were not considered. A large proportion of patients were excluded which may have resulted in sampling bias, and potentially missing those that suffered the most severe ADRs as they were too ill to consent. Events per variable (EPV) were not reported but could be calculated: 14 variables were considered and 115 events were identified and so the study failed to meet the recommended minimum of 10 EPV. The measurement of, and any blinding to the outcome were not clear.

Table 3.8 TRIPOD checklist: prediction model development as applied to the PADR-EC model

| Section/Topic | Checklist Item | Checklist item completed |
|---|---|---|
| **Title and abstract** | | |
| **Title** | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. | Partly<br>Study developing and/or validating multivariable model – No<br>Target population – Yes<br>Outcome to be predicted - Yes |
| **Abstract** | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | Partly<br>Objectives – No<br>Study design – Yes<br>Setting – Yes – broad i.e. hospital<br>Participants – yes – broad i.e. over 65years<br>Sample size – yes<br>Predictors – yes<br>Outcome – yes<br>Statistical analysis – no<br>Results – yes – frequency ADR, outcome of logistic regression and preventability reported<br>Conclusions - yes |
| **Introduction** | | |
| **Background and objectives** | Explain the medical context (including whether diagnostic or prognostic) and the rationale for developing or validating the multivariable prediction model, including references to existing models. | Partly<br>Medical context – yes, does not explicitly state that it is prognostic.<br>Rationale – yes<br>Reference to existing models - only 2 of 4 |
| | Specify the objectives, including whether the study describes the development or validation of the model or both. | No<br>Objectives – no, broad aim of developing and validating a model |

Table 3.8 cont. TRIPOD checklist: prediction model development as applied to the PADR-EC model

| Section/Topic | Checklist Item | Checklist item completed |
|---|---|---|
| **Methods** | | |
| **Source of data** | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. | Yes<br>Source data described – yes<br>Cohort study<br>Reported separately for development and validation |
| | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | Yes<br>Start and end of accrual – yes (Development = 12months, Validation = 4months) |
| **Participants** | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. | Partly<br>Study setting – yes, secondary care acute medical wards for development and validation. Number of wards not stated. |
| | Describe eligibility criteria for participants. | Yes<br>≥65 years, unplanned emergency admission to medical wards. Excluded if refused participation, unable to be interviewed, medical notes unavailable. |
| | Give details of treatments received, if relevant. | NA |
| **Outcome** | Clearly define the outcome that is predicted by the prediction model, including how and when assessed. | Partly<br>Outcome clearly defined – yes, ADR (WHO definition). Assessed by researcher (unknown qualifications). Medical record review and patient/relative interview.<br>ADR positive if known side-effect based on Australian Medicines Handbook, temporal relationship, after investigation other causes excluded.<br>Causality based on Naranjo. Only definite and probable included. |
| | Report any actions to blind assessment of the outcome to be predicted. | No<br>No blinding. Primary researcher collected data, screened for ADRs. Prospective study so variables selected prior to knowing outcome. Independent blinded senior clinical pharmacist screened all ADRs and 10% of non-ADRs. |

Table 3.8 cont. TRIPOD checklist: prediction model development as applied to the PADR-EC model

| Section/Topic | Checklist Item | Checklist item completed |
|---|---|---|
| **Predictors** | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured. | Yes<br>Medicines prior to admission – WHO ATC<br>Number of medicine – number of active ingredients<br>Clinical diagnosis – International Classification of Primary Care<br>Co-morbidity – Charleson Comorbidity Index<br>Renal failure – eGFR <60ml/min<br>Liver disease – raised ALT (twice normal range) or documented liver disease<br>Anaemia – Hb<120 female, <130 male<br>Comorbidities defined as present if documented in medical records.<br>Functionality – Barthel<br>PIMS – Beers<br>Recent changes to drugs – addition, deletion or change of dose in past 3 months, excluding PRN. (from interview) |
| | Report any actions to blind assessment of predictors for the outcome and other predictors. | None |
| **Sample size** | Explain how the study size was arrived at. | No<br>Not explained – convenience sample. No mention of need to have minimum EPV. |
| **Missing data** | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | No<br>Missing data outlined in table 2. Described the characteristics but unclear if from development or validation cohort. No detail with regarding handling. |

Table 3.8 cont. TRIPOD checklist: prediction model development as applied to the PADR-EC model

| Section/Topic | Checklist Item | Checklist item completed |
|---|---|---|
| **Statistical analysis methods** | Describe how predictors were handled in the analyses. | Yes<br>Variables identified using univariate analysis (Chi square or Fisher's exact test) were taken forward for binary logistic regression p<0.20<br>Multicollinearity between independent categorical variables assessed using phi coefficient. Two variables with phi ≥0.3 were trialled separately in model and one with highest predictive ability was retained. |
| | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | Partly<br>As per GerontoNet – stepwise logistic regression. Added and retained variables if p≤0.1. Method of elimination and retention unclear. Score developed as per GerontoNet – OR 1.00-1.49 =1, 1.5-2.49 = 2, 2.5-3.49 = 3 etc.<br>No internal validation. |
| | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | Partly<br>AUROC |
| **Risk groups** | Provide details on how risk groups were created, if done. | Not done |

Table 3.8 cont. TRIPOD checklist: prediction model development as applied to the PADR-EC model

| Section/Topic | Checklist Item | Checklist item completed |
|---|---|---|
| **Results** | | |
| **Participants** | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | Partly - development<br>1271 screened, 768 took part. 115 had ADR (Definite/Probable). 653 no ADR. Proportion doubtful/possible not reported.<br>Partly – validation<br>518 screened, 123 not willing, 155 too ill. 240 took part. 30 had ADR (definite/probable). 210 no ADR. Proportion of doubtful/possible not reported. |
| | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | Yes |
| **Model development** | Specify the number of participants and outcome events in each analysis. | Yes<br>Development 768 participants, 115 ADR<br>Validation 240 participants, 30 ADR |
| | If done, report the unadjusted association between each candidate predictor and outcome. | No<br>Adjusted OR reported for each candidate predictor and outcome. |
| **Model specification** | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | No<br>Regression coefficients and model intercept not reported. |
| | Explain how to use the prediction model. | No |
| **Model performance** | Report performance measures (with CIs) for the prediction model. | Partly<br>Only reported OR (95% CI) for variables included in model, AUROC and sensitivity and specificity at given cut point.<br>Calibration not reported |

Table 3.8 cont. TRIPOD checklist: prediction model development as applied to the PADR-EC model

| Section/Topic | Checklist Item | Checklist item completed |
|---|---|---|
| **Discussion** | | |
| **Limitations** | Discuss any limitations of the study (such as non-representative sample, few events per predictor, missing data). | Partly<br>Did not validate in community population.<br>Drug changes in past 3 months may have been inaccurate.<br>Variables from patient interviews may be subject to recall bias<br>Most unwell (and so at risk) patients may not be included as couldn't get consent.<br>Limitations do not discuss missing data, events per variables, clinical judgement variations on complex outcome. |
| **Interpretation** | Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence. | Yes |
| **Implications** | Discuss the potential clinical use of the model and implications for future research. | Yes |
| **Other information** | | |
| **Supplementary information** | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. | No |
| **Funding** | Give the source of funding and the role of the funders for the present study. | Yes |

Nair[68] produced a model which included six variables as outlined in Table 3.9; the predictive ability of this model was no better than the models identified in the systematic review, AUROC 0.70 (95% CI 0.65-0.75), sensitivity 72.2% and specificity 58%. External validation produced an AUROC 0.67 (95% CI 0.56-0.78), sensitivity and specificity 63%. The methods followed by Nair and colleagues[68] replicated that of Onder and colleagues[114] so it is perhaps unsurprising that the models perform similarly.

Table 3.9 Summary of PADR-EC model and scoring

| **Significant variables (multivariate analysis)** | **OR (95% CI)** | **Score** | **Validation** |
|---|---|---|---|
| Drug changes in the preceding 3 months | 1.54 (1.00-2.37) | 2 | External (n=240) |
| Renal failure (eGFR<60ml/min) | 1.97 (1.22-3.17) | 2 | Sensitivity 63% |
| Dementia | 2.44 (1.17-5.10) | 2 | Specificity 63% |
| Number of antihypertensives | | | AUROC 0.67 (95% CI 0.56-0.78) |
| 1-2 | 3.00 (1.22-7.38) | 3 | |
| ≥3 | 4.75 (1.89-11.93) | 5 | |
| Anticholinergics | 2.09 (1.16-3.75) | 2 | |

AUROC: area under the receiver operator curve; CI: confidence interval; eGFR: estimated glomerular filtration rate; OR: odds ratio

In addition to clinical and medication variables that the previous studies considered, Nair[68] included PIMS (according to Beers[57]), any recent changes to medications and groups of medications e.g. multiple antihypertensives. Univariate analysis also assessed associations between variable and outcome for: admission in preceding month or 3 months, use of dosing administration aid, use of generics, use of alcohol, smokers, presence of ADR within 3months, regular pharmacy visits, HMR in preceding 3months, assistance required with >1 activities of daily living (ADL). Many of these variables were not considered in the previous model development and, of these, drug changes in the previous 3 months was the only one that was retained in the final model. Whilst it is commendable to incorporate these previously "untested" variables, the authors failed to consider variables relating to the important concept of frailty in this population. None of the existing models have considered this and none have developed a model with good enough accuracy for use in clinical practice. The addition of frailty to a future model, measured using an easy to conduct assessment such as hand grip strength, may provide a level of accuracy that the models identified through this review are lacking.

## 3.7 Conclusions

Risk stratification is attractive, especially in older patients where the population is growing, placing an increased demand on the healthcare service - a service which is woefully underprepared for the projected global growth.[146] Models must be of high quality for clinicians to have confidence in their ability to predict risk with adequate sensitivity and specificity, especially in the case of ADR risk prediction models, a poorly researched area of risk prediction. Five ADR risk prediction models were identified with poor to modest performance, raising questions about their overall quality. Further work needs to be conducted on these existing models to develop a robust ADR risk prediction model which is externally validated, with practical design and good performance. Issues highlighted in this review were primarily in the study design and the approach used for evaluation: low sample size, lack of an independent validation sample, and little attention to recommended lists for assessing assumptions.

Four of the models were developed to address medication harm in the inpatient setting. The development of more models within this setting continues as outlined by the SENATOR Project, a pan-Europe collaboration which aims to develop computer software that will optimize medications and non-pharmacological interventions in multimorbid older adults.[147] Whilst this may be an important line of enquiry, identifying those at risk in the community or at the point of discharge from hospital may have more impact.[148] Transferring a patient between care settings is associated with a high-risk of harm, partly due to changes in patients' clinical status, medications and functionality, and the failure to effectively communicate such changes. The NHS National Reporting and Learning System recorded approximately 10,000 reports of patient safety incidents relating to discharge in one year (October 2012 – September 2013), with the most severe outcomes being death and avoidable re-admission to hospital.[149] The ability to identify those at risk of medication harm at this stage in the patient journey and focusing on costly medication related hospital re-admissions[2] could assist in the targeting of interventions and the delivery of more favourable outcomes.

## 3.8 Re-framing medication related harm – a potential conceptual framework

### 3.8.1 The need to move risk prediction research forward

The literature highlights many variables which are significantly associated with medication related harm with a large focus upon clinical variables, and individual or classes of medicines. Except for the number of medicines, the significance of most associations decreases or disappears when combined in a multivariate model, indicating potential multicollinearity between these previously studied variables. Furthermore, as outlined in the systematic review, when developed into a predictive model, only a moderate predictive ability is demonstrated. This research finding is supported by observations in clinical practice where not all older adults taking multiple medicines, with complex comorbidities, experience MRH. The focus of MRH research needs to move beyond the clinical and medicine-related variables and adopt a more holistic approach incorporating the psychological and social systems which influence medicines use.

It is notable from the literature that whilst a few studies have considered functional or social variables, for example independence in activities of daily living or alcohol consumption, the variables which influence how medicines are used have not been explored fully. These variables may include social support mechanisms, or factors influencing adherence to treatments such as depression. Perhaps it is only those who have risks, or deficits, across multiple systems (clinical, medicines and/or psychosocial) that are increasingly vulnerable to MRH. Parallels may be drawn between this theory and the concept of frailty. Scarcely considered in the context of MRH risk prediction research, frailty, said to be "the most problematic expression of population ageing", is recognised to increase an individual's risk of experiencing adverse health outcomes when exposed to an external stressor.[150] When this external stressor is a medicine, the outcome may be medication related harm.

Multiple models have been developed to measure frailty however, the phenotype model[151] and frailty index (FI)[152] dominate the literature. Two distinct instruments, the phenotype model focusses upon pre-defined signs and symptoms, in comparison to the FI which calculates the number of deficits accumulated from an unspecified set of criteria relating to disease and function.[153] Based on the principle "the more individuals have wrong with them, the higher the likelihood they will be frail"[154], it seems that there is a limit to the number of deficits. The maximum

FI compatible with life is 0.67. Clegg and colleagues[155] derived an electronic FI (eFI) for use in the community setting. In this study, the severity of frailty was categorised as patients with an eFI score of 0-0.12 were fit; >0.12-0.24 were mildly frail; >0.24-036 moderately frail and > 0.36 as severely frail. Estimated prevalence for each of these categories was 50, 35, 12 and 3%, respectively.

Cullinan and colleagues[156] recently tested the hypothesis that there is a relationship between frailty and potentially inappropriate prescribing (PIP) and ADR risk. They concluded that a patient with a frailty index (FI) of ≥0.16 is more than twice as likely to experience an ADR, stating that a FI could be a useful clinical indicator. The concept of frailty warrants further exploration in order to identifying potential variables associated with MRH.

### 3.8.2 Frailty and medication related harm

The physiological adaptions that occur with ageing and disease, and the resulting impact on the basic pharmacokinetics and pharmacodynamics of medicines, has been extensively described in the literature.[102] However, it is likely that the physiological changes only partly explain the risk of MRH in older adults as social and psychological factors may also contribute. This bears congruence with Rockwood and colleagues'[157] proposal that a definition of frailty should encompass not only medical but psychological and social factors too. Another similarity is the dynamic nature of MRH risk and frailty. As with frailty, a reduction in deficits are likely to be equally as important as the accumulation of deficits when considering the future risk of MRH and appreciating that risk can increase and decrease with time. Nicholson and colleagues[158] recently emphasised that whilst existing frailty models focus upon deficits, considering what a patient can do should not be overlooked. This salutogenic approach, meaning an approach which focuses upon factors which support health rather than purely focus upon disease[159], recognises the relevance of coping strategies and the resilience of older patients when challenged.[158] Figure 3.2 attempts to explain the complex interplay between the physiological and psychosocial systems and their likely influence on the occurrence of MRH.

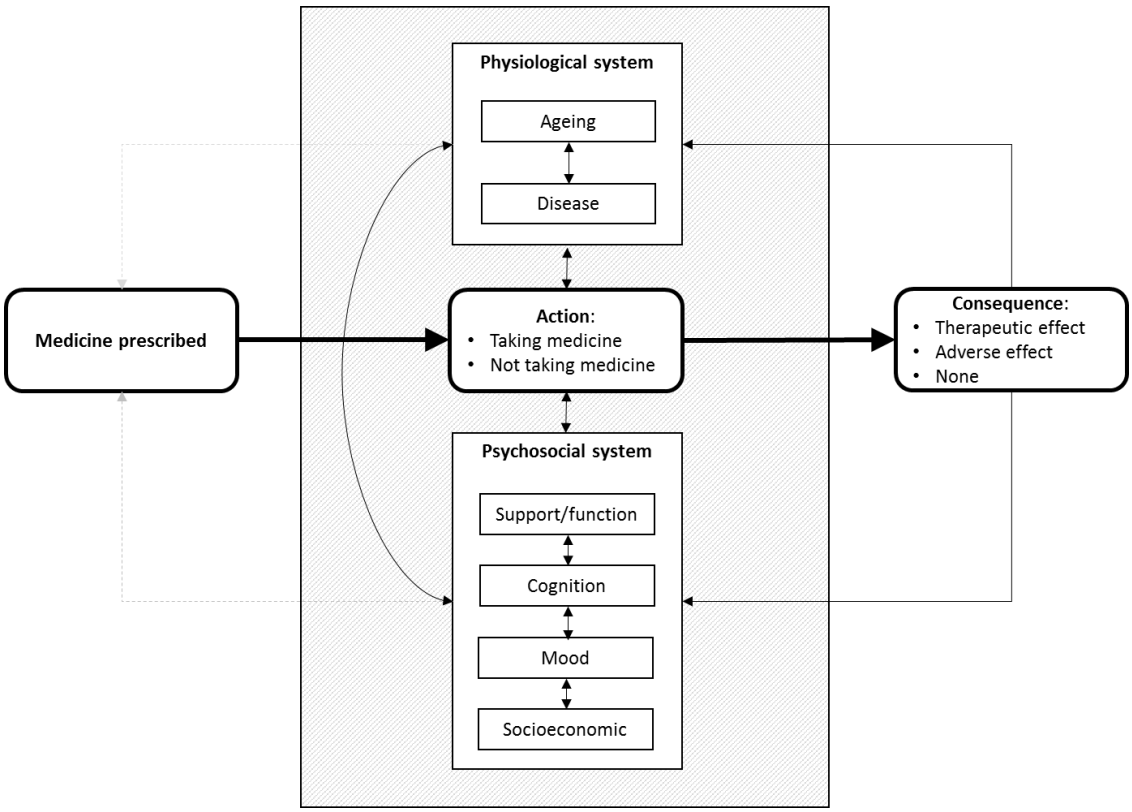



Figure 3.2 Proposed model outlining the relationship between age, disease, psychosocial issues and MRH

A simplistic linear visualisation of the journey from a medicine being prescribed, to the potential use by the patient (adherence or non-adherence), and the consequence of this action being a therapeutic effect, an adverse effect or no effect is presented, Figure 3.2. The journey is of course far more complex. The physiological and psychosocial systems which influence the action and the consequence of medicines use must be considered. Failure to consider these systems at the point of prescribing a medicine may result in MRH e.g. a patient with age-related renal impairment who is prescribed a medicine that is largely dependent upon renal excretion, such as gentamicin, is likely to experience increased plasma concentrations, resulting in MRH if a dose adjustment is not made at the point of prescribing. Similarly, a patient who is dependent upon a multi-compartment compliance aid (MCA) (colloquially referred to as a dosette box) for support with the administration of their medicine and is prescribed a medicine which cannot be added to the MCA (e.g. warfarin due to the variability in dosing), may experience MRH due to the omission of the medicine. These examples illustrate the potential relationship between the action of prescribing a medicine and the physiological and psychosocial systems which influence the outcome (efficacy

or adverse effects). Further exploration of this relationship is beyond the scope of this thesis which will focus on the post-prescribing period.

When considering the physiological system, it is necessary to discuss the concept of physiological reserve. An innate excess capacity of organs and biological systems, it is essential in maintaining physiological homeostasis. It is however limited, and may be overwhelmed by a substantial insult. Whilst physical, nutritional or lifestyle interventions for example may improve or preserve function, over the course of a lifetime the physiological reserve of an individual will decline. Different, but often linked, mechanisms i.e. ageing and/or disease (Figure 3.2) impact on the loss of reserve, the rate and chronology of which is subject to individual variation. A depletion of this reserve may increase the likelihood of adverse events, as seen in frailty.

With regards to MRH, adequate function of the physiological system will theoretically result in the expected therapeutic effect of a medicine when administered at a therapeutic dose. In contrast, a significant overdose of a medicine is likely to overwhelm the physiological reserve of any individual regardless of excess capacity. When a medicine is administered at an acceptable therapeutic dose to an individual with a depleted physiological reserve, the risk of harm due to the medicine is likely to increase, but will be dependent upon several factors including the drug pharmacology, the extent to which the physiological reserve is depleted, and which organs and biological systems are involved. An individual may tolerate a complex medicine regimen whilst there is a depleted, yet sufficient, physiological reserve, however the balance between tolerating the medicines and harm is likely to be very delicate. Any further insult, be it major or minor, to the physiological system may be enough to topple the balance, resulting in harm. This could, for example, be in the form of an acute infection, the addition or removal of a drug, or simply continued ageing. It may also be due to a reduction in the functional capacity of the psychosocial system.

The reserve, or excess capacity, within the psychosocial system is influenced by a wide range of factors some of which include functional ability, social support, cognition, mood or financial circumstances and, as outlined in Figure 3.2, the function of the physiological system. As an example, poor health due to disease resulting in impaired physiological function can reduce mood, and thus psychosocial reserve, and *vice versa*. As with physiological reserve, an individual may tolerate a complex medicine regimen even when the psychosocial reserve is depleted, however

a minor insult may result in significant harm. The fragility of this balance may be likened to the vulnerability of a frail older person to even minor insults as outlined by Clegg and colleagues[150] whereby the initiation of a new drug for example may result in a disproportionate level of harm.

In addition to the influence of the physiological and psychosocial systems, it would also seem plausible that the consequence of a previous action feeds back to impact directly on future actions and also on the capacity of the physiological and psychosocial systems. For example, a patient with depleted physiological and psychosocial systems due to severe chronic obstructive pulmonary disease experiences oral thrush secondary to an inhaled corticosteroid. As a result they become non-adherent to their inhaler which results in a further decline in respiratory function and a reduction in mood which in turn influences future actions with detrimental consequences.

A further complexity is polypharmacy. Where a patient is prescribed multiple medicines, elucidating the causal factor becomes increasingly challenging, as highlighted by the many interacting pathways in Figure 3.3.

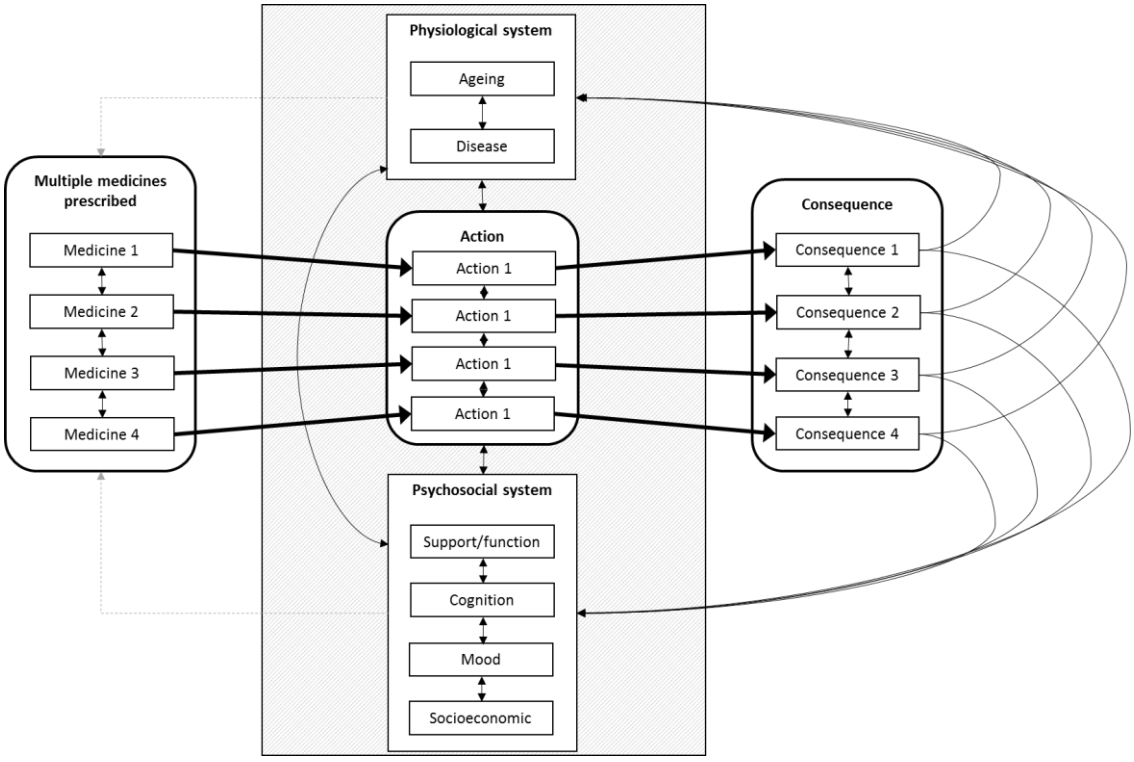



Figure 3.3 Interaction between systems, action and consequences in a patient prescribed multiple medicines

In such a complex system, it is difficult to conclusively associate a specific medicine with an observed harm. This represents a significant challenge when conducting MRH risk research as

the misappropriation of blame may occur. Such misclassification of events will influence the level of significance of the associations of variables and MRH, and thus the accuracy of the predictive model in which they are incorporated.

It is likely that multiple factors; medicine related, physiological and psychosocial, contribute to MRH but the extent to which is debatable. With increasing age comes increasing heterogeneity, making the identification of universal MRH risk prediction variables even more challenging.

### 3.8.3 Medication related harm, a geriatric syndrome?

A concept which successfully identifies global risk factors in an older population is that of geriatric syndromes. Consisting of delirium, falls, frailty, dizziness, syncope, and urinary incontinence, Inouye and colleagues[160] define the concept of geriatric syndromes and their multifactorial nature and shared risk factors. Like frailty, they argue that geriatric syndromes defy traditional medical practice due to the requirement to look beyond the biological model and consider social, spiritual and financial domains. The numerous potential pathways leading to the manifestation of a geriatric syndrome, and the interaction between these pathways, is complex and cannot be compartmentalised, for example to a single body system. It may be argued that this is similar to MRH where, as already described, multiple causes contribute to an outcome.

The reported shared risk factors of geriatric syndromes include; old age, cognitive impairment, functional impairment and impaired mobility. Inouye and colleagues propose a combined conceptual model whereby geriatric syndromes lead to frailty which in turn, through shared risk factors, cause geriatric syndromes (see Figure 3.4).

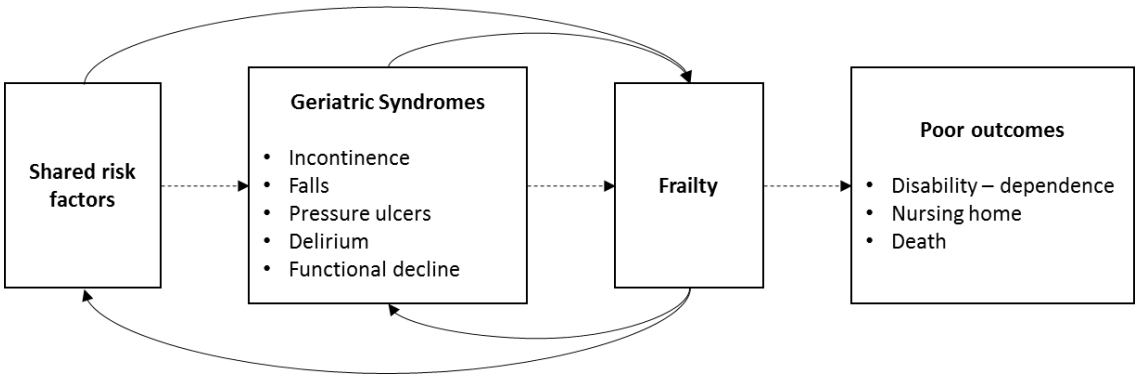



Figure 3.4 Conceptual model developed by Inouye and colleagues demonstrating shared risk factors potentially leading to geriatric syndromes and frailty

It is proposed that given the commonality that exists between geriatric syndromes (and thus frailty) and MRH, that MRH may be considered a geriatric syndrome. Where previous studies have demonstrated an association between polypharmacy and geriatric syndromes[161], here it is proposed that it is MRH that is the geriatric syndrome rather than polypharmacy. In order to investigate this hypothesis it is necessary to explore associations between the frailty risk factors and MRH, with the aim of identifying key risk prediction variables for MRH. Only then can the development of a predictive model for MRH with greater accuracy than those already identified in the literature be attempted.

### 3.8.4 Outcome of MRH

Over and above the severity of MRH, the level of physiological and psychosocial reserve may influence the type of healthcare utilised as a consequence of harm. The salutogenic approach described earlier supports the theory that the same insult experienced by different individuals may have a different outcome, depending upon their coping strategies (which are related to their physiological and psychosocial reserve). A relatively minor insult in the form of harm from a new medicine may result in the self-management of harm in one individual, but may require healthcare utilisation, for example hospitalisation, of another, as illustrated in Figure 3.5.

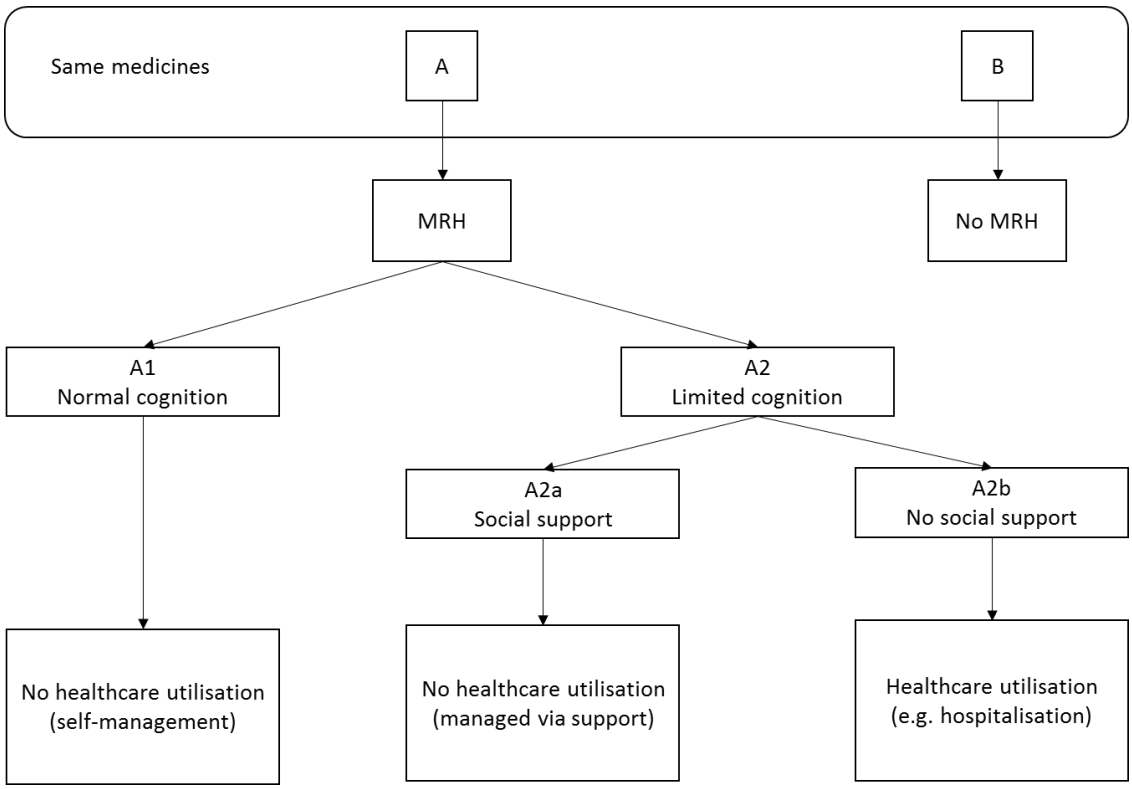



Figure 3.5 Case example illustrating that the same insult (medicines) to different individuals may have a different outcome

Therefore, whilst the level of healthcare utilisation secondary to MRH is of interest, it should be kept in mind that a particular type of MRH is unlikely to predict the type of healthcare utilisation sought. The exception may be in the most severe form of MRH where physiological and psychosocial systems are completely overwhelmed and hospitalisation is required.

## 3.9 Summary

This work highlights that although numerous factors have been associated with MRH, we may need to consider the occurrence of MRH more in line with frailty and/or geriatric syndromes. The proposed conceptual framework (Figure 3.3) will be referred to in Chapter 4 and Chapter 5 as a way of explaining the occurrence and causes of MRH seen in our study population.

# Chapter 4 Prospective cohort study

## 4.1 Introduction

Hospitalisation due to MRH reflects significant morbidity and is costly to the NHS. A recent systematic review of studies conducted in the acute care setting and published between 2003 – 2013 investigated ADRs causing admission of patients aged 65 years old or over. Across the 14 studies included in the review, a median prevalence of ADR related hospitalisation was 10% (95% CI: 7.2%–12.8%).[122] Whilst there are many studies reporting hospitalisation secondary to ADRs, few have explored the incidence of MRH during the post-discharge period. A review of European ADR observational studies published from January 2000 onwards, found only 5 papers reporting the ADR rate in the outpatient setting - none of which focussed on older adults.[11] Another review, using an outcome definition of post-discharge drug related problems, Garcia-Caballos and colleagues'[24] concentrated on studies with a population age of over 60 years old. The reported incidence of post-discharge MRH ranged from 18.4-37.5% and, where reported, a third were preventable[26]. No study exploring post-discharge MRH in a frail older population has been conducted in the UK.

At a time when patients are at an increased risk of adverse outcomes[23], an understanding of the incidence, severity and causality of MRH during the post-discharge period may help to guide medicine optimisation strategies in older adults. As outlined in Chapter 3, there are many studies which have investigated inpatient ADRs and ADEs in an attempt to develop models to predict those most at risk of harm[18,85,88,89]. One study focussed on the risk of hospital admission due to ADRs.[68] The poor to moderate accuracy of these models is perhaps the result of concentrating on clinical and medicine related variables. Whilst important variables when considering harm from medicines, the conceptual framework presented in Chapter 3 (Figure 3.3) suggests that they are not fully representative of the multiple and diverse range of variables that can influence an individual's risk of adverse outcomes. Likened to frailty, and geriatric syndromes, it is proposed that MRH does not have a clearly defined cause but is influenced by physiological, psychological and social parameters. These parameters are likely to interact synergistically and so exploring psychosocial variables in addition to physiological variables is important in order to advance our ability in identifying those at risk of MRH. Furthermore, the frequency and type of healthcare accessed in relation to MRH is likely to be influenced by these variables too.

Older adults are four times as likely to be hospitalised due to an ADR compared to younger people[39] but the healthcare utilisation associated with post-discharge MRH is unknown. It is likely that whilst hospitalisation is the most costly outcome of MRH, and therefore worthwhile investigating, the frequency of community based care associated with MRH will be high.

Little is known about post-discharge MRH in older adults, although it is suspected to commonly occur and have significant impact on the healthcare system. The ability to identify those at risk of post-discharge harm could improve the efficiency of the healthcare provided to this population, but needs to consider factors outside the traditional clinical or medicines-related domains.

## 4.2 Aim and objectives

The aim of this observational study was to explore MRH experienced by older adults following discharge from an acute inpatient episode in a UK hospital. The objectives were:

1. Assess the frequency, causality, severity and preventability of MRH during the 8-weeks post-discharge from hospital.
2. Determine the frequency of healthcare episodes related to post-discharge MRH.
3. Describe the medicines most commonly causing MRH.

## 4.3 Methods

### 4.3.1 Research setting

This research was undertaken over a 24-month period (December 2013 – December 2015) on the acute older persons' unit (OPU) at St. Thomas' Hospital, part of GSTFT. GSTFT is a large inner-city London hospital trust, with over 1200 hospital beds, offering emergency and specialist care to the local boroughs of Lambeth and Southwark (44% of inpatients) and beyond (38% and 18% of inpatients are from the rest of London and UK respectively). Lambeth and Southwark are amongst the most deprived local authorities within the UK, ranking 14$^{th}$ and 25$^{th}$ out of 326 areas on the Index of Multiple Deprivation. Approximately a third of over 60 year olds live in income deprived households.[162]

### 4.3.2 Population

The OPU accounts for approximately a third (36.7%) of general medical beds at St. Thomas' Hospital and consists of three wards (84 beds). Upon admission to the hospital, patients are triaged by a specialist geriatric multidisciplinary team. This team allocates OPU beds on the basis of availability and need. A review of patient need is conducted by the specialist team around nine domains, outlined in Table 4.1. Therefore, patients admitted to the OPU are selected on the basis of multimorbidity and frailty, both factors likely to increase the incidence of MRH. For example, most patients admitted to the OPU will have "deficits" in at least four domains described.

Table 4.1 Referral criteria for admission to OPU

| **Domain** | **Rationale for selection for a specialist OPU** |
|---|---|
| Age | Normally over 70 years old (younger if medically old/frail e.g. due to stroke or Parkinson's Disease. Majority are over 80 years old. |
| Cognitive function | Dementia or delirium - high priority. |
| Continence | Incontinence and/or difficulties with elimination in general e.g. constipation, urinary retention. |
| Mobility | Poor mobility - higher priority to those with a sudden decline and probable potential for reversibility. |
| Falls risk | Falls of unknown cause requiring investigations and observations. |
| Pressure care/complex wounds | Multiple causes, indicative of increased nursing care and nutritional needs. |
| Nutrition | Poor swallow resulting in high-risk of aspiration, malnourished and become very frail when they are ill. |
| Complex medical issues | Often incurable, degenerative conditions such as chronic obstructive pulmonary disease or heart failure. |
| Complex social issues | Higher priority going to those whose needs are not being met in the community. |

#### 4.3.2.1 Inclusion criteria

Patients had to be over the age of 65 years at the time of recruitment and registered with a GP within Lambeth, Southwark or Westminster Clinical Commissioning Groups (CCGs). These localities were selected as they included the majority of patients admitted to the OPU whilst keeping the geographical spread of GP practices manageable for the follow up data collection phase. The locality of the patient's GP practice was obtained from the patient's electronic records and confirmed with the patient during recruitment to the study.

#### 4.3.2.2 Exclusion criteria

Patients were excluded from the study if they did not consent to participate in the study; lacked capacity and did not have a personal consultee; were transferred to another acute healthcare trust (excluding transfer to an intermediate care facility) or; had a short life expectancy and were therefore unlikely to survive to the end of study eight week follow up period.

Capacity, in accordance with the Mental Capacity Act 2005[163], was assessed by the research nurse or research pharmacist who had undertaken capacity and consent training. It was recognised that seeking consent from this population may present some issues: many older patients suffer fluctuating or temporary loss of capacity upon admission to hospital due to delirium; some older patients may lack capacity for the duration of the study; gaining consent may be unsettling, creating confusion as they will not experience change in their clinical care. Previous studies in this area have not consented participants however they have not studied primary care utilisation or self-reported medication related problems.[164] It is important that primary care utilisation is investigated as this outcome measure has rarely been studied in the field of medication harm in older adults and is likely to be contribute to increased workloads and pressure on services.

Patients with a short life expectancy were identified as those who had been place on the AMBER Care Pathway. Recommended by the Department of Health, and developed at GSTFT, this care bundle is designed to improve the quality of care of patients where recovery is uncertain and, although they are still receiving active treatment, they are at risk of dying in the next 4-8 weeks.[165]

### 4.3.3 Patient recruitment

The patient recruitment and data collection process are outlined in Figure 4.1. Patients medically fit for discharge from the OPU were screened against the inclusion criteria and, where eligible, were invited to participate in the study by the research nurse or pharmacist. The principles of the Declaration of Helsinki were upheld, and patients were provided with verbal and written study information and allowed a minimum of 24 hours to decide if they wished to participate. Written consent (or assent) was obtained from all participants. Where a patient lacked capacity to consent, their next of kin was asked to act as a personal consultee and to support their relative taking part in the study. It was important to include those who lacked capacity, as failure to do so

could exclude those who are potentially most likely to experience MRH i.e. those most vulnerable due to frailty and/or cognitive impairment. Where a potential participant lacked capacity and the next of kin was unavailable, they were excluded from the study. Patients who consented to be included in the study were assigned a Unique Patient Identifier Number (UPIN) which was used throughout the data analysis to maintain patient confidentiality.

### 4.3.4 Data collection process

A standardised CRF was designed by the principal researcher to capture all relevant data. Up to three data sources (the clinical records, the patients/carers and the direct care team) were used to generate the most accurate patient data.

Baseline admission and follow up data were collected by the principal researcher, research nurse or pharmacist using the CRF. Details of the baseline data collected are described later in this chapter and are summarised in Figure 4.1.

The follow up data collection process (Figure 4.1) was conducted 8 weeks after discharge from hospital by the principal researcher and included a review of up to three sources: 1. Patient interview; 2. GP records review and; 3. Re-admission review (where applicable).

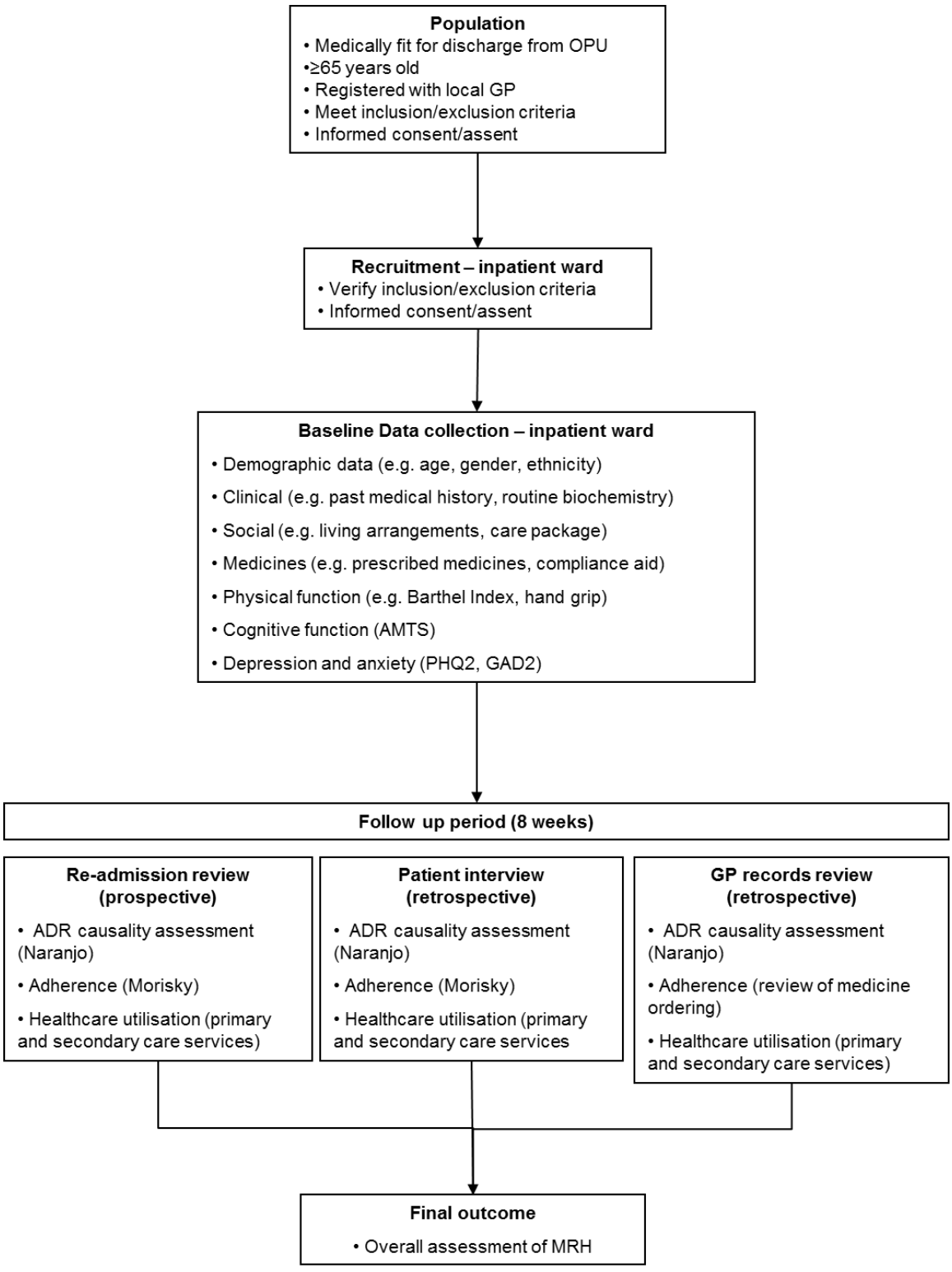



Figure 4.1 Patient recruitment and data collection flowchart

### 4.3.5 Standardisation of data to be collected

The possible data to be collected and the outcomes to be assessed, were identified by the principal researcher and verified by an expert panel following the steps outlined in Figure 4.2.

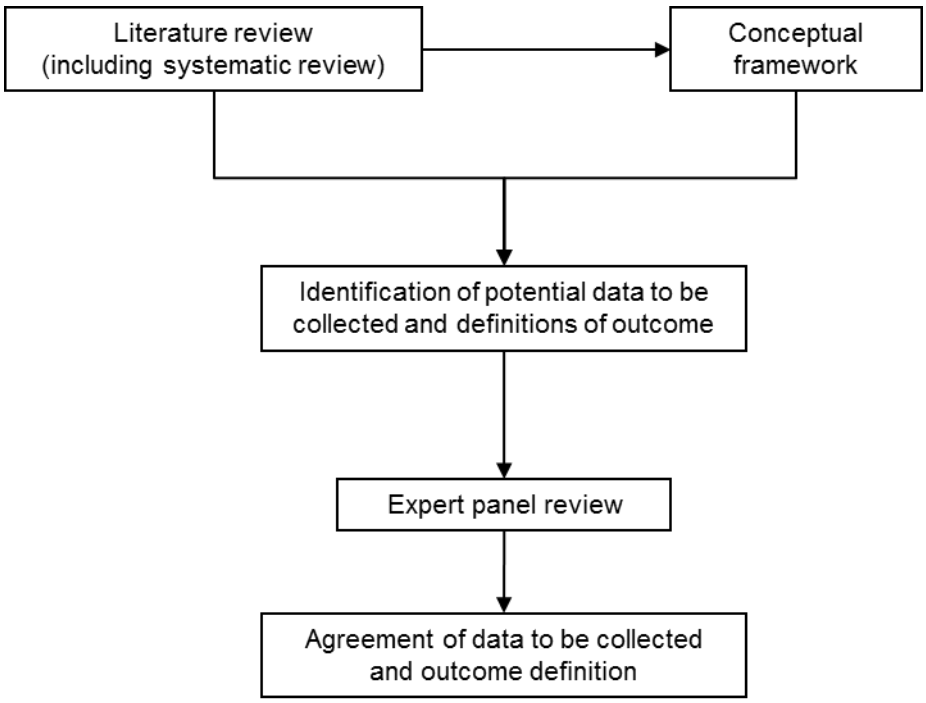



Figure 4.2 Process of identification and selection of data to be collected and agreement on definition of outcome

Following a comprehensive review of the literature by the principal researcher, including a systematic review to identify existing MRH risk prediction models, a conceptual framework was developed as described in Chapter 3 (Figure 3.3). In summary, where previous studies have focussed on clinical and medicine related risk variables, it is proposed that both physiological and psychosocial variables are equally important when considering the risk of an older person experiencing MRH. This is consistent with the key domains that are believed to contribute to frailty.[157] The link between frailty and harm from medicines is supported by Cullinan and colleagues[156] where, in a study of 711 older inpatients, it was concluded that those with a FI of ≥0.16 were twice as likely to experience an ADR.

From the literature, a list of potential variables, including previously studied MRH risk variables and variables associated with frailty, was generated (Appendix C). The list was emailed to an

expert panel two weeks prior to meeting to determine the data to be captured. The panel of local and international experts consisted of:

- 2 professors of geriatric medicine (UK and Netherlands)
- 2 consultant geriatricians (UK)
- 1 professor of clinical pharmacy and therapeutics (UK)
- 2 clinical pharmacists specialising in older people (UK)

The expert panel reviewed all variables for their clinical relevance and consistency with the literature. They considered and agreed for each potential MRH risk variable: the importance (essential, desirable, not important); the timing and frequency of collection (for example, on admission or discharge); the source of the data; if there was an existing measure used in practice for example, the Barthel Index as a measurement of activities of daily living; whether the potential MRH risk variable had been included in an existing MRH risk prediction model; and ultimately if the variable should be included. Variables deemed non-significant following assessment by univariate analysis in previous studies were not immediately discounted; their significance was reviewed by the expert panel. This is recognised practice and is especially important if the dataset is small or the variable rare.[109] Agreement on the potential MRH risk variables to be collected was reached through discussion. Basic demographic data to be collected was agreed.

### 4.3.6 Baseline data

Data collected for all patients included demographic (e.g. age, gender, ethnicity), clinical (e.g. presenting complaint, discharge diagnosis, co-morbidities, renal and hepatic function, biochemistry), medicines (e.g. name, dose, frequency and use of a compliance aid), length of stay and social information (e.g. care package provision, support with medicines and living arrangements).

Where possible, validated instruments, used routinely on the OPU were used to collect data such as nutritional status, functional ability, cognitive function and depression and anxiety as outlined in Table 4.2. The utilisation of instruments used in routine care should improve the transferability of any future risk prediction model developed. The assessments were conducted by the research nurse/pharmacist and, where appropriate, the OPU nurse caring for the patient. Training was

provided to ensure consistency of assessment. Questions in the abbreviated mental test score (AMTS), patient health questionnaire (PHQ-2) and general anxiety disorder score (GAD-2) were asked as written to reduce any subjectivity.

Table 4.2 Validated assessments used in data collection

| Variable of interest | Validated assessment | Who conducted assessment |
|---|---|---|
| Nutritional status | MUST[166] | Research nurse/pharmacist |
| Function ability | Barthel ADL[121] | Research nurse/pharmacist/OPU nurse |
| Frailty measure | Hand grip[167] | Research nurse/pharmacist |
| Cognitive function | AMTS[168] | Research nurse/pharmacist |
| Depression | PHQ-2 questionnaire[169] | Research nurse/pharmacist |
| Anxiety | GAD-2 questionnaire[170] | Research nurse/pharmacist |

ADL: Activities of Daily Living; AMTS: Abbreviated Mental Test Score; GAD-2: General Anxiety Disorder-2; MUST: Malnutrition Universal Screening Tool; OPU: Older Persons Unit; PHQ-2: Patient Health Questionnaire-2

#### 4.3.6.1 Nutritional status

Many validated and widely used tools are available for the screening of malnutrition in clinical practice including, the Subjective Global Assessment (SGA)[171], Mini-Nutritional Assessment (MNA)[172] and Nutrition Risk Screening (NRS)[173] and the Malnutrition Universal Screening Tool ('MUST')[166]. The SGA, MNA and NRS all require the patient's weight, which can be difficult to obtain in the busy clinical environment, the 'MUST' does not. It is also the nutritional screening tool recommended by the British Association for Enteral and Parenteral Nutrition (BAPEN) and used on the OPU at St. Thomas' Hospital and so was used for this study. The score ranges from 0-2, with 0 indicating low, one medium and two a high malnutrition risk. All patients scoring 2 are referred to the dietician for assessment and treatment.

#### 4.3.6.2 Functional ability

The modified Barthel ADL index is a 10 item (20 point) score used to measure the performance of activities of daily living.(13) Originally developed to measure rehabilitation progress, it is commonly used to assess disability in the acute clinical environment.[174] Studies investigating its reliability when used in the older population are limited and a systematic review concluded that it's accuracy may be reduced in those with cognitive impairment when assessment via physician interview and nurse observation are compared.[174] The studies however are too few and small to draw robust conclusions. When compared to the Katz ADL it was suggested to be the more

appropriate index for the acute care setting[175] and is the measurement of ADL used on the OPU at St. Thomas' and also for this study.

#### 4.3.6.3 Cognitive function assessment

An extensive range of cognitive function assessment tools are described in the literature including the MMSE, Mini Cog and the 6-item cognitive impairment test (CIT) for example, each measuring different aspects of cognitive impairment and each with advantages and disadvantages.[176] The abbreviated mental test (AMTS) measures cognition on a scale of 0 (poor) to 10 (excellent), where a score of <8 is suggestive of cognitive impairment.[168] It was chosen as the method for assessing cognition in this study due to its brevity, taking approximately 2 minutes to complete, no requirement for any props or writing by the patient and reported sensitivity (91%) and specificity (82%) using a cut off <8 when compared to MMSE.[177] The assessment was conducted as close to discharge as possible to reduce the impact of acute illness on cognitive function.

#### 4.3.6.4 Depression and anxiety assessments

PHQ-2 and GAD-2 are recommended by NICE for the screening of populations at high-risk of depression or those with chronic ill health[178] and the screening of anxiety respectively.[179] Both were derived from longer diagnostic tools; PHQ-9 for depressive disorders and GAD-7 for anxiety disorders. They each consist of two questions that focus on the core symptoms of the disorders and enquire about the frequency of these symptoms over the previous two weeks. Respondents have 4 options; "not at all", "several days", "more than half the days", "nearly every day", scoring 0, 1, 2, 3 respectively. The total scores for the PHQ-2 and GAD-2 can therefore range from 0-6, the higher the score the greater the likelihood of suffering the relevant disorder.[169,170] Widely reviewed and commonly used in the community setting, the PHQ-2's accuracy in the acute care setting, and in particular its use in older adults requires further investigation.[180] Similarly, the GAD-2 has demonstrated validity in a community based older population but further validation studies are required.[181,182] For the purpose of this study however, the brevity, endorsement by NICE and widespread use in the NHS made them the measures of choice.

#### 4.3.6.5 Hand grip

Hand grip strength has been identified as a quick, easy and reproducible measure of muscle strength and has been recommended in the screening process of sarcopenia, a syndrome characterised by progressive loss of skeletal mass and strength and often present in frail older adults.[183,184] It was measured using the JAMAR Hydraulic Hand Dynamometer by the research nurse or pharmacist who were trained using the Southampton Protocol for Adult Grip Strength Measurement. This protocol formed part of a review paper that identified the JAMAR Hydraulic Hand Dynamometer as the most widely used instrument for measuring grip strength with excellent inter-rater reliability.[167,185]

#### 4.3.6.6 Co-morbidities and diagnoses

Comorbidity has long been recognised as an important consideration in medical statistics.[186] This importance has arguably grown as an increasing proportion of the population are living with multiple long term conditions[44] and comorbidities may impact upon the outcome of interest. Designed as a measure of prognostic co-morbidity for longitudinal studies in 1987, the CCI[187] is widely used in clinical research and was used as the measure of comorbidity in this study. It consists of 19 conditions each weighted according to its ability to predict 1 year mortality. Weightings range from 1 (e.g. myocardial infarction) to 6 (e.g. metastatic cancer). The sum of the weightings for the conditions identified in the patient are calculated. The higher the score the greater the comorbidity and predicted 1 year mortality: score 0, 12% 1 year mortality; 1–2, 26%; 3–4, 52%; and ≥5, 85%. The CCI has been criticised for the fact that it does not consider the severity of several conditions in its weighting system. For example, a patient with mild heart failure will be attributed the same score as a patient with severe heart failure and so risks missing the extent of this as a potential predictor of mortality.[188] However, with good test-retest and inter-rater reliability, good predictive validity demonstrated for many outcomes[189], clearly defined conditions[190] many of which have been associated with ADR related hospitalisation[191], it was identified as an appropriate measure. Data required to complete the CCI was obtained from the patient's medical records and through discussion with the direct medical team and the patient or carer during the admission.

Discharge diagnoses were obtained from the Electronic Discharge Letter (EDL). All diagnoses, not just primary diagnosis, were included in the analysis. It is recognised that following the introduction of Payment by Results by the Department of Health, England, whereby hospital trusts are paid by healthcare commissioners for each patient seen based upon the complexity of the case[192], there may be a temptation to "engage in opportunistic behaviour" or "gaming"[193] of the system and so overstate the complexity of the diagnosis. A recent study quantifying the prevalence of frailty in English hospital would suggest that this is not the case. They found that the coexistence of multiple frailty syndromes was uncommonly coded.[194] Due to the complexity of the patients recruited to this study, where many conditions are linked and impact upon one another, it was necessary to use all discharge diagnoses and not just the primary diagnosis.

#### 4.3.6.7 Biochemical parameters

The association of biochemical parameters and ADRs has been identified in several studies.[19,89] The results of tests conducted as part of routine clinical care were recorded on admission and discharge, where admission results were those taken within 48 hours of admission and discharge results were those taken as close to discharge as possible. Where a test was not conducted or a result not available the data were recorded as missing. The following parameters were collected, where available, for every patient:

- Full blood count (white cell count, haemoglobin, platelets, neutrophils, lymphocytes)
- Inflammatory markers (C reactive protein)
- Electrolytes and renal (sodium, potassium, urea, creatinine, eGFR)
- Liver (alanine transaminase, alkaline phosphates, bilirubin)
- Metabolic (albumin, glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides)

#### 4.3.6.8 Medicines

The total number of medicines taken at the time of admission and on discharge were recorded, including name, dose and frequency. It was also recorded if an MCA filled by a healthcare professional was used by the patient. To obtain the most accurate list of medicines, admission medicines were recorded after the completion of medicines reconciliation by the ward pharmacist.

Medicines reconciliation is a process where a patient's pre-admission medicines are identified and compared with the medicines they are currently prescribed and any unintended discrepancies rectified within 24-hours of admission. This includes the use of OTC medicines.[72] Medicines at discharge were recorded from the ward pharmacist approved EDL. All medicines were coded by the research pharmacist using the World Health Organisation Anatomical Therapeutic Classification (WHO-ATC) code. A seven character internationally recognised coding system, the WHO-ATC classifies a drug at five levels as described in Table 4.3.

Table 4.3 WHO-ATC drug classification system (using diuretics as an example)

| Level | Group | Code | Description |
|---|---|---|---|
| 1st | Anatomical main group | C | Cardiovascular |
| 2nd | Therapeutic main group | C03 | Diuretics |
| 3rd | Therapeutic/pharmacological subgroup | C03C | High-ceiling diuretics |
| 4th | Chemical/therapeutic/pharmacological subgroup | C03CA | Sulphonamides |
| 5th | Chemical substance | C03CA01 | Furosemide |

### 4.3.7 Main outcome measure

The primary outcome of the study was to determine the incidence of MRH occurring during the eight-week period following discharge from the OPU. The definition of MRH is outlined later in this chapter. Causality, preventability and severity were also determined and will also be defined.

The secondary outcome was to measure the healthcare utilisation due to MRH during the follow-up period. This was measured with the aim of quantifying the number of healthcare episodes that were due to MRH. Furthermore, the proportion of preventable MRH related healthcare episodes was also calculated to allow identification of potentially unnecessary healthcare utilisation. A count of accident and emergency (A&E) attendance, hospital admission, GP consultation, contact with out of hours services and visits to a community pharmacist for advice or treatment regarding MRH was used to determine healthcare utilisation. Patients could have multiple healthcare episodes with the same or different services for a single episode of MRH e.g. a patient may at first seek advice from their GP but is ultimately admitted to hospital. This would count as two episodes of healthcare. Where a patient attended A&E and was admitted directly to the hospital this counted as one healthcare episode and was classified as an admission.

#### 4.3.7.1 Definition of primary outcome measure

As reported by Leendertse and colleagues[34], when researching harm due to medicines, the definition of the outcome measure impacts on the prevalence of harm reported. Frequently, and incorrectly, ADE and ADR are used interchangeably. ADE describes harm from a medicine and includes errors in prescribing, dispensing and administration.[6,7] ADR refers to harm when a medicine is used at an established dose for an appropriate indication.[8]

Three common definitions of adverse drug events, adverse drug reactions and medication related problems (Table 4.4)[6–8,195–200] were presented to the previously described expert panel. Based on these existing definitions, through discussion, a standardised definition for this study was agreed.

Table 4.4 Definitions of medicines related harm

| Term | Definition | Sub-classification |
|---|---|---|
| Adverse Drug Events (ADE) (Bates et al.)[6] | "An injury resulting from medical intervention relating to the drug"[6] | 1. ADRs<br>2. Medication errors<br>3. Therapeutic failures<br>4. Adverse drug withdrawals<br>5. Overdoses[7] |
| Adverse Drug Reactions (ADRs) (World Health Organisation)[8] | "A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function."[8] | Type A: Augmented<br>Type B: Bizarre<br>Type C: Chronic<br>Type D: Delayed<br>Type E: End of use<br>Type F: Failure[195–199] |
| Medication (Drug) Related Problems (Strand et al.)[200] | "Drug related problem is an event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care"[200] | 1. Untreated Indication<br>2. Improper Drug Selection<br>3. Subtherapeutic Dosage<br>4. Failure to Receive Drugs<br>5. Overdosage<br>6. Adverse Drug Reaction<br>7. Drug Interaction<br>8. Drug Use without Indication[200] |

The definitions provided for ADE and ADR were rejected by the panel as being too broad in the case of ADE and too narrow in the case of ADR. The agreed definition of the primary outcome measure was derived from the Strand and colleagues definition of medication related problems.[200] It was selected on the basis that it more accurately reflects the presentation of MRH in older adults in clinical practice. When investigating a complex older population, harm from medicines is likely to involve ADRs and difficulties with accessing or using medicines. This is captured in the definition of the primary outcome of this study, medication related harm (MRH), which focussed on harm due to:

- "Failure to receive drugs - The patient has a medical problem that is the result of his or her not receiving a drug (e.g. for pharmaceutical, psychological, sociological or economic reasons)", including failure in the supply chain and problems with adherence.
- "Adverse drug reaction - The patient has a medical problem that is the result of an ADR" defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function."[8]

Similar to the outcome measure presented by Hallas and colleagues[130], abnormal laboratory results and non-adherence without clinical symptoms were not included in this study. This is in contrast to Gandhi and colleagues[201] who considered some abnormal laboratory values to be ADEs even if there was no symptomatic problem. It is acknowledged that asymptomatic abnormal laboratory values have the potential to cause harm, however it would be only be due to clinical need that bloods were conducted and the abnormal values identified.

#### 4.3.7.2 Outcome data

It is recognised that the reporting of medication harm, more specifically ADRs, is poor amongst healthcare professionals and patients.[6,202,203] The consequence of this under-reporting is reflected in studies investigating ADRs and ADEs where medical chart review yields a higher prevalence than spontaneous reporting or database screening methods.[34] Ruiz and colleagues found only 34.6% of all ADRs identified in a prospective cohort study were later identifiable retrospectively using the ICD coding from the hospital discharge report.[164] Furthermore, incidents were not always recorded in the patient notes, especially in the outpatient setting, and so it was concluded that eliciting information from the patient themselves is important.[22]

Using only self-reporting techniques however, may result in data skewed towards minor, unconfirmed reports with multiple proposed "culprit" medicines, whilst using only healthcare professional reports may miss the less severe MRH events.[204]

Gandhi and colleagues used telephone interviews to follow patients up and compared the overlap with computer systems, self-reporting by healthcare professionals, and chart review. Patient interview identified 92% of ADEs in the outpatient setting in comparison to 28% by chart review. Overlap occurred in only 19% of cases reviewed and so the use of multiple methods appears to be complimentary and useful in determining the true event rate.[201]

To overcome the limitations of each data source described in the literature and capture a true incidence and range of severity of MRH, multiple approaches were used to determine MRH in this study: patient self-reporting, computer system review, healthcare professional identification and medical chart review.

#### 4.3.7.3 Patient interview (self-reported MRH)

Eight weeks after discharge the patient and/or carers were contacted via telephone by the principal researcher. A minimum of three (and maximum of 20) attempts at contact were made within the ten-week post-discharge period after which, if contact was unsuccessful, the patient was deemed lost to follow up for the self-reported MRH part of the study. A two-week window was incorporated to allow for individuals who were, for example, on holiday.

A standardised questionnaire was used to conduct a semi-structured interview with the patient and/or carer. They were asked about their general health and healthcare utilisation over the 8 weeks after discharge (pharmacist and GP contact, Out of Hours contact, hospital attendance/re-admission) and whether they had recognised any unwanted side effects from their medicines. Patient adherence to their discharge medicines was measured using the Morisky Adherence Rating Score (MARS)[205] (Table 4.5). Consisting of four questions, each answered yes or no, MARS measures the likelihood of an individual being adherent to their medicines on a scale of 0-4. The higher the score, the more likely the patient is adherent.

Table 4.5 Morisky Adherence Rating Score questions and scoring system

| **Question** | **Response (score)** |
|---|---|
| Do you ever forget to take your medicine? | Yes (0) / No (1) |
| Are you careless at times about taking your medicine? | Yes (0) / No (1) |
| When you feel better do you sometimes stop taking your medicine? | Yes (0) / No (1) |
| Sometimes if you feel worse when you take your medicine, do you stop taking it? | Yes (0) / No (1) |

#### 4.3.7.4 GP records review (Primary Care MRH)

Using a standardised data collection form, the principal researcher reviewed the patient's GP records for the eight-week follow up period to determine whether the patient had experienced any MRH and had, as a consequence, required additional healthcare. Dates of issue and re-ordering of medicines were reviewed to determine an estimated level of adherence to prescribed medicines.

#### 4.3.7.5 Re-admission review (Secondary Care MRH)

To identify if a patient had been re-admitted during the 8-week follow up period, daily reviews of hospital admissions were undertaken by the research nurse or pharmacist. In the event of a re-admission the research nurse/pharmacist collected baseline re-admission data (which included the same data as the original baseline data) using the standardised data collection form. The principal researcher interviewed the patient and/or carer to determine any non-adherence using the MARS and reviewed the patient's medical notes and blood results, in conjunction with the admitting Consultant, to determine if the re-admission was due to MRH. In the event that agreement could not be reached between the Consultant and the pharmacist, the case was presented by the research pharmacist to the study End Point Committee (EPC) for discussion and a final decision. The EPC consisted of a Consultant geriatrician and Professor of Clinical Pharmacy and Therapeutics.

### 4.3.8 Determining MRH

A two-step process was applied to identify and confirm cases of MRH (Figure 4.3). The first step, the initial assessment, was conducted by the principal researcher (and consultant physician where relevant). The second step, the final classification of MRH was made by the study EPC.

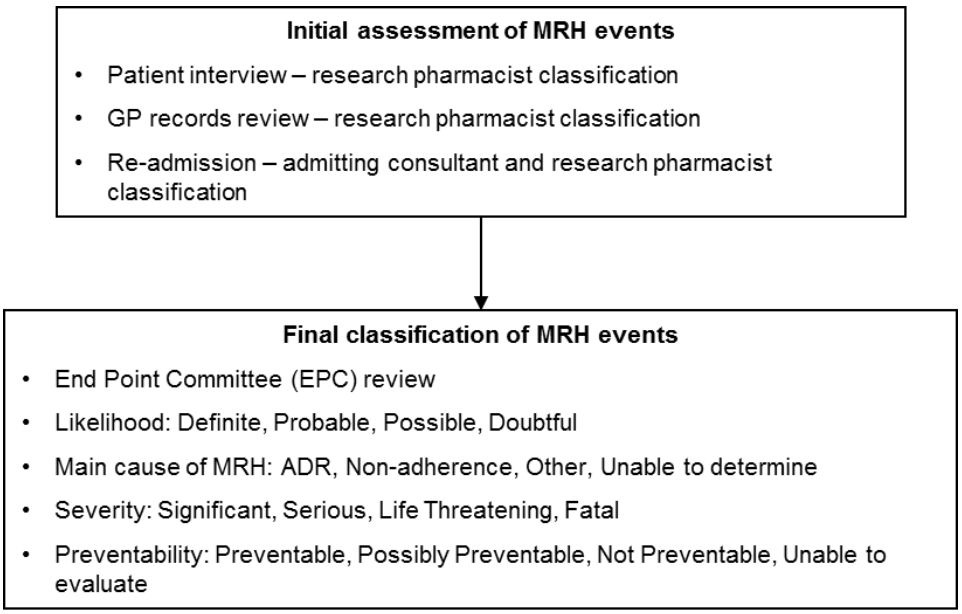



Figure 4.3 Confirmation and classification of MRH

#### 4.3.8.1 Initial assessment of MRH outcomes

Key information required to support the principal researcher (and Consultant physicians where relevant) in determining the likelihood that the patient had experienced MRH included current medicines, assessment of medicines adherence (using MARS), history of presenting complaint, ADR profile of the prescribed medicines, relevant comorbidities and appropriate clinical observations and investigations.

Table 4.6 provides details of how the outcome of the initial assessment was recorded. Further details outlining the definitions of causality, severity and preventability are described below.

Table 4.6 Key questions and answer options used to record MRH

| **Question** | **Options** |
|---|---|
| 1. Do you think this patient has suffered medication related harm? | Definite, probable, possible, doubtful |
| 2. How confident are you in this judgement? | Little or no confidence, slight to moderate confidence, <50% confidence but a close call, >50% confidence but a close call, strong confidence, virtually certain |
| 3. If the patient has suffered medication related harm, what was the main cause?<br>- What medicines were implicated?<br>- What was the clinical event? | ADR, non-adherence, other, unable to determine<br><br>- Free text entered by the research pharmacist<br>- Free text entered by the research pharmacist |
| 4. If the patient has suffered medication related harm, was it preventable? | Definitely, possible, not preventable, unable to determine |
| 5. If the patient has suffered medication related harm, what was the severity? | Fatal, life threatening, serious, significant |

#### 4.3.8.2 Causality

Where an ADR was suspected, the Naranjo algorithm[129] was utilised to support the causality assessment. Reproducible assessment of causality is important when studying ADRs to produce consistent measurement of the outcome of interest. A systematic review identified 34 assessments using three main methods, expert judgement, probabilistic approaches and, most commonly, algorithms.[206] Each method has advantages and disadvantages and all require some level of clinical judgement potentially limiting their reproducibility. As there is no universally accepted assessment this study followed the algorithm based approach, in conjunction with expert opinion. The Naranjo algorithm was selected based on its use in previous studies investigating in-hospital ADRs and hospitalisation secondary to ADRs.[2,14] Published in 1981, the

Naranjo algorithm was developed with the aim of reducing inter-rater variability when assigning causality to potential ADRs, and so improving pharmacovigilance. In a study of 6 raters (2 physicians and 4 pharmacists) inter-rater reliability was reported to improve from Kappa=0.21-0.40 to Kappa=0.69-0.86 when the algorithm was applied to a set of 63 patient cases.[129] Consisting of 10 weighted questions (see Table 4.7), causality is classed as definite (score ≥9), probable (score 5-8), possible (score 1-4) and doubtful (score ≤0). The Naranjo algorithm rates causality conservatively as many of the questions are not relevant e.g. did the same reaction occur when a placebo was administered? Furthermore, the often atypical and non-specific presentation of MRH in older adults and the multimorbidity frequently present makes it difficult to definitively attribute causality to a specific medicine(s). Therefore, it was used as a guide to ensure a temporal association, previous reports of the reaction and other possible causes were all considered when determining MRH due to an ADR, in conjunction with expert opinion. Causality was categorised into four categories: definite, probable, possible and doubtful.

Table 4.7 Naranjo algorithm questions and associated scores

| **Question** | **Yes** | **No** | **Don't know** |
|---|---|---|---|
| 1. Are there previous conclusive reports on this reaction? | +1 | 0 | 0 |
| 2. Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 |
| 3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 |
| 4. Did the adverse reaction reappear when the drug was re-administered? | +2 | -1 | 0 |
| 5. Are there alternative causes (other than the drug) that could on their own have caused the reaction? | -1 | +2 | 0 |
| 6. Did the reaction reappear when a placebo was given? | -1 | +1 | 0 |
| 7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 |
| 8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | +1 | 0 | 0 |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 |
| 10. Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 |

#### 4.3.8.3 Severity

The severity of MRH was graded using ratings defined by Morimoto and colleagues.[22] The four categories were fatal, life threatening, serious and significant as described in more detail in Table 4.8.

Table 4.8 Classification and definition of severity of MRH

| Severity | Definition |
|---|---|
| Fatal | Patient died due to the incident |
| Life threatening | Requiring hospitalisation resulting in permanent defects or life-threatening complications |
| Serious | Additional visit to clinic for treatment or additional medications, including dose reductions or cessation of therapy |
| Significant | Any significant event that is identified by the patient but not requiring a change in therapy |

#### 4.3.8.4 Preventability

It is widely accepted that medicines, even when used in accordance with present day knowledge of good medical practice, may cause harm that could not be prevented. Whilst it is important to remain vigilant in order to limit the severity of such harm, efforts may be better spent focussing on preventable MRH. It is therefore important when studying MRH that preventability is considered. The most commonly used preventability criteria for ADR/ADE studies, derived by Hallas and colleagues.[130] and outlined in Table 4.9, were applied to all cases of suspected MRH.

Table 4.9 Classification and definition of preventability of MRH

| Classification | Definition |
|---|---|
| Definitely preventable | Treatment inconsistent with current knowledge of good medical practice or was unrealistic taking circumstances into account. |
| Possibly preventable | Prescription was not erroneous but the event could have been avoided by an effort exceeding the obligatory demands. |
| Not preventable | Could not have been avoided by any reasonable means, or it was unpredictable during treatment fully in accordance with good medical practice. |
| Unevaluable | Rating could not be obtained or evidence was conflicting. |

### 4.3.9 Confirmation and classification of MRH

For all patients, the outcomes recorded for each follow up stage (i.e. telephone interview, GP records review and re-admission review, where applicable) were reviewed by the principal researcher and a senior clinical academic pharmacist to determine the final outcome. Likelihood, preventability, severity, main cause (i.e. ADR, non-adherence or both), the nature of the event and the medicine(s) involved were determined (Figure 4.3). Any disagreement was resolved

through discussion. This form of mixed methods, using healthcare professional reporting and identification of ADR by members of the research team and verification through a systematic medical review by a panel of experts, has been adopted in previous ADRs studies.[122] The total number of events due to MRH were recorded.

### 4.3.10 Healthcare utilisation

The healthcare utilisation, that is the number of re-admissions, A&E attendances, access to out of hours services, GP or pharmacist contacts for each stage of the follow up were also reviewed by the principal researcher and senior clinical academic pharmacist. Due to the complex presentation of this population it can often be difficult to determine one definite cause for healthcare utilisation therefore it was not possible to state that MRH caused the presentation but in all cases it contributed to it. The agreed count of MRH related episode of care was recorded.

### 4.3.11 Recording of data

Screening, recruitment and follow up data logs were recorded using Microsoft Excel and were password protected. The CRF was developed using Formic Solutions version 5.51 build 005 computer software. Using this software data were scanned from the paper CRF into an electronic database which was cleaned and transferred into SPSS for analysis. CRFs were stored in a locked cabinet, in an office with restricted access, for the duration of the study.

### 4.3.12 Sample size

A sample size of 1500 patients was calculated for the PRIME Study (see Chapter 2, Section 2.5). As this thesis was a sub-analysis of the St. Thomas' cohort a separate sample size calculation was not conducted and the cohort investigated was therefore a convenience sample.

### 4.3.13 Analysis

Descriptive statistics were applied to describe the primary and secondary outcomes and the population characteristics. Categorical data were presented as number (%) and numeric data as

mean (SD). Non-normally distributed numeric data were presented as median (inter-quartile range (IQR)). The analysis was undertaken using the SPSS software (version 24.0; SPSS, Inc., Chicago, IL, USA).

### 4.3.14 Approvals and funding

The study was approved by the National Research and Ethics Service, East of England (Norfolk; REC reference 13/EE/0075) (Appendix D) and was funded by the Guy's and St. Thomas' Charity (G100716) and the National Institute of Health Research (NIHR) – Research for Patient Benefit (RfPB) (PB-PG-0711-25094). The study was adopted as a Clinical Research Network Portfolio study (Ageing and Primary Care). Local Research and Development Departments approvals were obtained prior to study commencement.

## 4.4 Results

### 4.4.1 Patient recruitment

Over the study period 8280 patients were discharged from the three wards of the OPU. Of these, 1122 patients were screened for participation in the study, of whom 857 met the criteria for inclusion and 421 patients were recruited to the study. Not all patients were screened due to limited resources; screening was not possible at weekends or during public holidays, and staff had to prioritise re-admitted study patients due to short lengths of stay, resulting in reduced time for screening patients.

Of the 701 patients not included, consent or assent was not given or could not be obtained in 436 (62%). The remaining patients were outside of the designated GP catchment area (n=153), had a short life expectancy (n=95), were under 65 years old and were admitted to the OPU due to bed pressures (n=13) or were not ready for discharge (n=4). Twenty-five patients were later withdrawn: 17 had already taken part in the study and had been re-admitted after the 8-week follow up period, three had not been discharged by the recruitment closure date, three died before they were discharged, and two of the patient's GPs were found to be outside the designated catchment area for follow up (Figure 4.4).

Consequently, 396 patients completed the 8-week follow up and formed the study cohort.

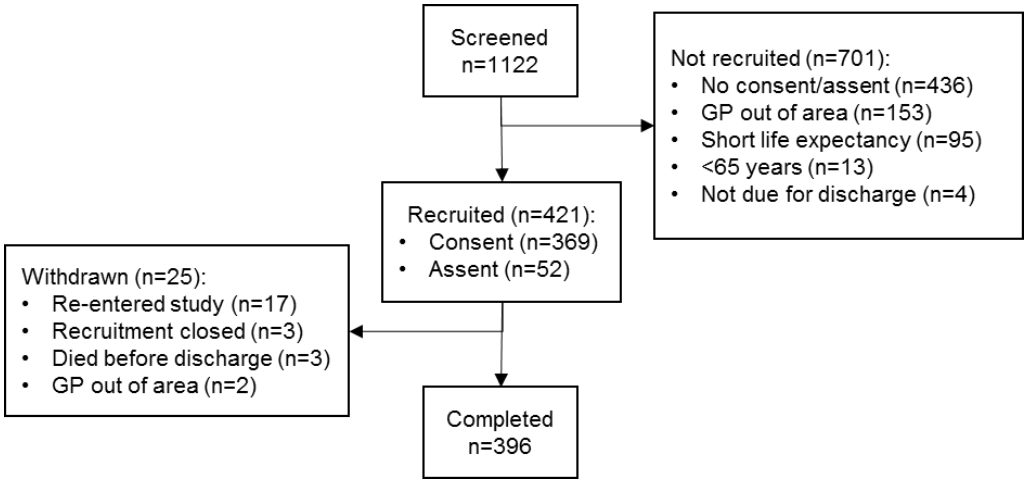



Figure 4.4 Screening and recruitment

### 4.4.2 Demographics

The demographics of the study cohort compared to the general OPU population and those patients screened for inclusion are outlined Table 4.10. There were some variations in demographics between the three groups. A larger proportion of females were recruited to the study (64.7%) than were screened for the study (61.2%) or discharged from OPU in general (59.8%).

Table 4.10 Description of OPU, screened and study populations

| **Demographic** | **Study cohort (n=396)** | **Screened population (n=1122)** | **All OPU discharges (2014-16) (n=8280)** |
|---|---|---|---|
| Gender (female) (%) | 256 (64.7) | 687 (61.2) | 4954 (59.8) |
| Age > 85 years (%) | 175 (44.1) | 502 (44.8) | 3787 (45.7) |
| Ethnicity (white) (%) | 352 (88.9) | - | 6586 (79.5) |

OPU: Older Persons' Unit

The study cohort was predominantly white, reflecting the cohort of very old inner Londoners, and not as diverse as the overall patient population. According to the 2011 Census, less than half the all-age population (approx. 45%) of Lambeth would described themselves as White British.[46] The ethnicity of the older population in London however appears to be less varied. Data published by the Greater London Authority for 2015 estimated that approximately 70% of residents in Lambeth, Southwark and Westminster aged 65-90 years old were described as White.[207] The older population discharged from the OPU in 2014-16 are even more ethnically homogeneous (79.5% White) and the study cohort even more so still. Only 11.1% of study participants were not White which may be reflective of language barriers limiting recruitment to those who have English as a first language.

A similar proportion of patients over the age of 85 were recruited to the study (44.1%), as were screened (44.8%) and discharged from the OPU generally (45.7%). The mean age of patients recruited to the study was 83 years old (65-102 years, SD 7.0), see Figure 4.5. Patients over the age of 80 years old formed almost 69% of the study population, with the majority (52%) aged between 80-90 years old. This age distribution is reflective of the selection criteria, outlined earlier, for admission to the OPU. Importantly, it also characterises a frequently underrepresented segment of society in clinical trials.[208]

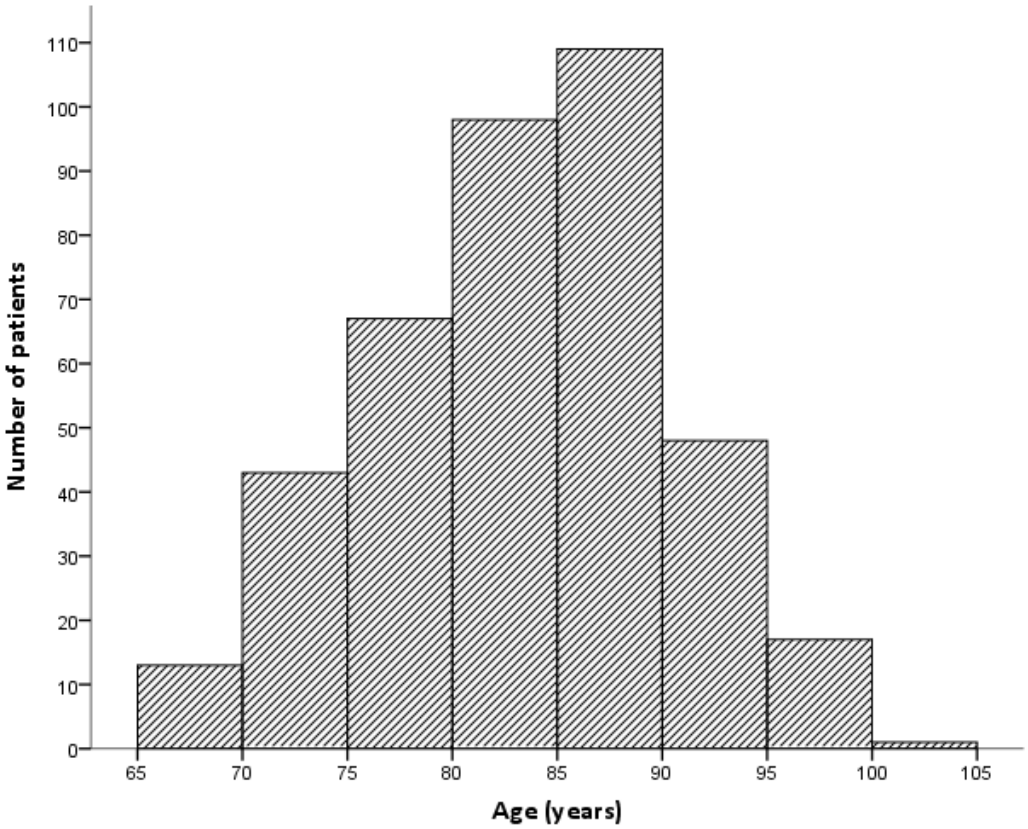



Figure 4.5 Age distribution of study population

Further baseline demographics of the study cohort are outlined in Table 4.11 and are grouped loosely around four domains of the Comprehensive Geriatric Assessment (medical, mental health, functional capacity and social circumstances).[209] In summary, the cohort may be described as multimorbid, and although cognitively intact, they have impaired functional capacity and most are dependent upon formal care. The overall demographics are suggestive of a frail older population.

Table 4.11 Baseline demographics, including clinical, frailty, social parameters of study participants (n=396)

| Variable | | Number of patients (%) |
|---|---|---|
| **Demographics** | | |
| Female | | 256 (64.7) |
| Mean Age (years) (SD) | | 83.3 (7.0) |
| Ethnicity: White | | 352 (88.9) |
| **Medical** | | |
| Mean CCI (SD) | | 2.16 (1.63) |
| Mean number of conditions (SD) | | 4.53 (1.87) |
| Median eGFR (ml/min/1.73m$^2$) (IQR) | | 64 (45, 82) |
| Mean number of discharge medicines (SD) | | 10.07 (4.37) |
| Median length of stay (IQR) | | 10 (6, 17) |
| MUST: | 0 | 209 (55.0) † |
| | 1 | 72 (19.0) † |
| | 2 | 99 (26.1) † |
| **Mental Health** | | |
| Mean AMTS (SD) (range 0-10)[a] | | 8.29 (1.71) |
| Mean PHQ-2 (SD) (range 0-6)[b] | | 1.74 (1.87) |
| Mean GAD-2 (SD) (range 0-6)[c] | | 2.26 (2.04) |
| **Functional capacity** | | |
| Hand Grip: | <20kg (Female) | 225 (88.6) ^ |
| | <30kg (Male) | 128 (91.4) |
| Falls: | 0 | 119 (30.1) ˜ |
| | 1 | 91 (23.0) ˜ |
| | 2 | 185 (46.8) ˜ |
| Mean Barthel Index (SD) (range 0-20) | | 13.24 (4.56) |
| **Social circumstances** | | |
| Living arrangements: | | |
| Lives alone | | 262 (66.3) |
| Lives with spouse/family/friend/carer | | 124 (31.4) |
| Lives in an institution | | 9 (2.3) |
| POC Frequency: | | |
| 0 | | 146 (36.9) |
| 1-3 | | 108 (27.3) |
| >4 times per day (incl. 24 hr home care) | | 111 (28.0) |

AMTS: abbreviated mental test score; CCI: Charlson comorbidity index; eGFR: estimated glomerular filtration rate; GAD: generalised anxiety disorder; IQR: inter-quartile range; PHQ: Patient Health Questionnaire; POC: package of care; SD: Standard Deviation;

[a]: higher score = better cognition; [b]: higher score = more likely depressed; [c]: higher score = more likely anxious; † missing data (n=380); ^ missing data (n=254); ˜missing data (n=395)

#### 4.4.2.1 Medical

The study cohort had a mean CCI of 2.16 (SD 1.63), equating to a 26% one year mortality rate. As described in more detail in Chapter 5, 37 patients died during the 8-week follow up period, suggesting a potentially higher mortality rate than is reflected by the mean CCI. It should however be noted that after an acute event deaths are not evenly spread over 12 months.[210] The number of conditions and discharge medicines may provide a better indication of the level of comorbidity in the study population, being 4.53 (SD 1.87) and 10 (SD 4.37) respectively. Co-morbidities were dominated by diseases of the cardiovascular system; most commonly hypertension (diagnosed in 61.4% of the study population), atrial fibrillation (26.3%) and hyperlipidaemia (22.7%). Connective tissue disorders (including rheumatoid arthritis, osteoarthritis and systemic lupus erythematous), obstructive lung disease and diabetes were also common and were diagnosed in 29.8%, 28.5% and 27.3% of the study population respectively. The median renal function, measured by eGFR, was 64 ml/min (IQR 45,82), with under half (44%) of all patients being described as renally impaired (eGFR <60ml/min). Nutritional impairment was identified in 45% of the cohort as determined by a MUST score of ≥1.[211] The most frequent discharge diagnosis, based on body system, were those relating to the musculoskeletal system (including falls, fractures and reduced mobility) (25.8%), the respiratory system (including COPD, pneumonia and pulmonary emoboli) (23.8%) and the cardiovascular system (including heart failure, atrial fibrillation and postural hypotension) (17.4%).

#### 4.4.2.2 Mental Health

The majority (74%) of patients were cognitively intact with an AMTS ≥8 (mean 8.29 (SD 1.71)). Anxiety and depression levels were low, mean GAD-2 2.26 (SD 2.04) and mean PHQ-2 1.71 (SD 1.87), both below the recommended screening cut-off of 3.[169,170]

#### 4.4.2.3 Functional capacity

There was impairment in all measures of functional capacity. The mean hand grip stratified by gender was; females 12.21kg (5.79), and males 19.93kg (7.28). 89% females and 91% males would be described as sarcopenic using the cut offs recommended by the European Working Group on Sarcopenia in Older People (EWGSOP)[184], as outlined in Table 4.11.

#### 4.4.2.4 Social circumstances

Almost 80% lived in privately owned or rented accommodation, with most living alone (66%). Only eight patients were nursing home residents. Social support, in the form of a package of care, was provided to more than half of the study population (55%), and ranged from once daily visits to 24-hour live in care.

#### 4.4.2.5 Medicines

The mean number of medicines on admission was 8.8 (SD 4.40, range 0-25) and increased to 10.1 (SD 4.37, range 0-26) on discharge. Approximately 61% of patients were discharged home with more medicines and almost all patients were discharge with a change to their admission medicines, 384 (96.9%). This includes any medicines stopped or started but does not include changes in doses. New medicines were started in 355 (89.6%) patients; the number of new medicines ranged from 0-16 per patient.

Just over a quarter of the study population reported a previous ADR (102 patient (25.8%)). Approximately a third (33.2%) of patients, when asked, reported some degree of non-adherence illustrated by a MARS of less than four.

Support with medicines was common with 226/268 (84.3%) reporting help with medicines in the form of obtaining a supply 219/268 (81.7%) and/or administration 122/268 (45.9%). Help was most frequently provided through formal routes i.e. the pharmacy or formal carers arranging the supply of medicines (132/219 (60.3%)) and formal carers supporting administration of medicines (64/122 (52.5 %)). MCAs were used by 172 (45.9%) patients. Almost all patients 390 (98.7%) used only one community pharmacy to access their medicines.

A total of 3986 medicines were prescribed on discharge. The most commonly prescribed group of medicines, based on the WHO-ATC anatomical group classifications were medicines used to treat disorders of the alimentary tract and metabolism (25.8%), followed by cardiovascular system (20%) and nervous system (16.2%). Alimentary tract and metabolism medicines commonly included; laxatives (e.g. senna and macrgols), proton pump inhibitors (e.g. omeprazole), oral hypoglycaemic agents (e.g. metformin and gliclazide) and calcium and vitamin D supplements. The frequency of prescribing medicines used to treat gastric acid related disorders was higher

than the proportion of patients diagnosed with such conditions. It is likely that this reflects prophylactic prescribing to reduce the risk of gastrointestinal bleeding in those taking medicines such as antithrombotics (e.g. aspirin, clopidogrel, rivaroxaban) or prednisolone, which accounted for 8% of all prescribed medicines. Of all prescribed medicines, paracetamol was the most common, received by 60% of the study population at discharge.

### 4.4.3 Incidence of MRH

Of the 396 patients completing the 8-week follow up, 128 (32.3%) were unavailable for telephone interview and 10 patients did not have their GP review completed due to incorrect GP details. In all patients, at least one of the follow up sources was available i.e. telephone interview, GP records review or re-admission review. Three sources were available for 84 patients (21.2%), 2 sources for 284 (62.6%) patients and 66 (16.7%) patients had only 1 follow up source available.

Within the study cohort 158 of 396 (39.9%) patients experienced MRH within the 8-weeks follow up period, rated as possible, probable or definite; 113 experienced only 1 MRH event (71.5% of all MRH events); 34 (21.5%) experienced 2 MRH events; and 11 (7.0%) experienced 3 or more MRH events. In total 217 MRH events were identified. The rate of MRH is described in Table 4.12.

Table 4.12 Rates of MRH during 8-weeks follow up

| | **Number (%)** | **Event rate per 100 patients** |
|---|---|---|
| Total number of patients with MRH | 158 | 39.9 |
| Total number of MRH events | 217 | - |
| **Severity of MRH** | | |
| Fatal | 4 (1.8) | 1.0 |
| Life threatening | 2 (0.9) | 0.5 |
| Serious | 185 (85.3) | 46.7 |
| Significant | 26 (12.0) | 6.6 |
| **Preventability of MRH** | | |
| Definitely or possibly preventable | 126 (58.1) | 31.8 |
| Not preventable | 90 (41.5) | 22.7 |
| Unable to evaluate | 1 (0.5) | 0.3 |

The number of events based on severity and preventability of MRH are also outlined in Table 4.12. A total of 6 events were classified as life-threatening or fatal and will be discussed in more detail later in this chapter. Over half of all events were deemed preventable (58.1%); 26 were

definitely preventable, 100 possibly preventable. Due to conflicting information, it was not possible to evaluate the preventability of 1 event.

Approximately two thirds of MRH was due to ADRs (149 (68.7%)), 48 (22.2%) due to non-adherence, and 20 (9.2%) due to a combination of ADR and non-adherence. Examples of each are provided in Figure 4.6.

| |
|---|
| **Case 1: ADR**<br><br>Likelihood MRH: definite, Severity: serious, Preventable: definitely<br><br>93 year old male. Lives with niece. Past history of IHD, CCF, hypertension and BPH. After showering, central heavy chest pain. Took 2 puffs of GTN spray, felt dizzy so went downstairs. Niece found patient unresponsive in chair. Ambulance service stood patient up and witnessed 2nd episode of unresponsiveness lasting 3 minutes. No confusion, tongue biting or urinary incontinence. Similar episode in March 2013 due to oral ISMN which was then stopped but GTN spray was not reconciled in drug history and so patient continued to use. Diagnosed with syncopal episode after using GTN spray. |
| **Case 2: Non-adherence**<br><br>Likelihood MRH: definite, Severity: serious, Preventable: definitely<br><br>88 year old female. Lives alone, daily carer, supportive family. Past history of heart failure, COPD and dementia. Presented with increased shortness of breath and bilateral leg swelling. Discharged 7 days previously with increased bumetanide dose. At home carer administered medicines from old MCA containing lower dose of bumetanide. Symptoms responded well to increased diuretics. Diagnosed with worsening heart failure due to administration of incorrect dose of bumetanide. |
| **Case 3: ADR and non-adherence**<br><br>Likelihood MRH: definite, Severity: serious, Preventable: possibly<br><br>90 year old female. Lives alone, family provide care. Past history of AF, diabetes, PVD, reduced mobility, intermittent constipation, grade 3 pressure sore (ankle and buttock), recent #NOF. Daughter requested GP visit. Mum complaining of nausea and constipation. No urinary symptoms, negative MSU. Prescribed buprenorphine patch and dihydrocodeine from hospital (discharged 6 days previously) following #NOF. Has Laxido but does not take it. Diagnosed with constipation secondary to opioids and non-adherence to laxatives. |
| IHD: ischaemic heart disease; CCF: congestive cardiac failure; BPH: benign prostate hypertrophy; GTN: glyceryl trinitrate; ISMN: isosorbide mononitrate; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; MSU: midstream urine; PVD: peripheral vascular disease; #NOF: fractured neck of femur |

Figure 4.6 Case studies demonstrating MRH due to ADR, non-adherence and, ADR and non-adherence

#### 4.4.3.1 Type of MRH

The most frequently affected body system due to MRH was the alimentary system 68 (31.3%), followed by the central nervous 34 (15.7%) and haematological 20 (9.2%) systems. A summary of all MRH events, the body system affected and examples of the medicines involved is provided in Table 4.13. Constipation (n=25), falls (n=17), diarrhoea (15) and bleeding (15) were the most prevalent types of MRH.

Table 4.13 MRH event by body system and examples of commonly involved medicines (n=217)

| **System (%)** | **MRH event** | **Examples of medicines commonly involved** |
|---|---|---|
| Autoimmune (0.9) | Flare of phemphigiod (1), immunosuppression (1) | Prednisolone |
| CNS (15.7) | Behaviour change (1), black out (1), confusion (4), dizziness (3), drowsiness (2), hallucinations (2), headache (1), insomnia (2), low mood (1), nightmares (1), uncontrolled pain (11), sedation (1), seizure (1), stroke (1), tremulous (1), vivid dreams (1) | Dihydrocodeine, bisoprolol, warfarin |
| CVS (7.8) | AF (1), exacerbation HF (5), hypotension (2), peripheral oedema (2), postural hypotension (4), syncope (2), tachycardia (1) | Furosemide, spironolactone, ramipril |
| Dermatological (5.1) | Alopecia (1), puritis (2), rash (5), urticaria (1), varicose eczema flare (1), worsening eczema (1) | Cefalexin, rivaroxaban, emollients |
| Endocrine (4.1) | Hyperglycaemia (3), hypoglycaemia (6) | Insulin, gliclazide, prednisolone |
| Fall (7.8) | Fall (17) | Codeine, lorazepam, ramipril |
| Alimentary (31.3) | Abdominal cramps (1), black stools (4), constipation (25), diarrhoea (15), dry mouth (5), dysphagia (1), hepatotoxicity (1), nausea (6), overflow diarrhoea (1), stomach pain (1), taste disturbance (2), vomiting (5), worsening ascites (1) | Buprenorphine, senna, amoxicillin |
| Genito urinary (1.8) | Polyuria (1), urinary incontinence (1), urinary retention (2) | Furosemide, tiotropium |
| Haematology (9.2) | Bleeding (15), bruising (3), epistaxis (1), haematuria (1) | Warfarin, rivaroxaban, aspirin |
| Infection (5.5) | C. difficile (2), conjunctivitis (1), oral thrush (6), vaginal thrush (2), worsening infection (1) | Amoxicillin, Seretide |
| Musculoskeletal (1.8) | Fatigue (2), hip fracture (1), weakness (1), | Carboplatin, prednisolone |
| Renal (4.1) | AKI (5), hyperkalaemia (2), hypokalaemia (2) | Furosemide |
| Respiratory (4.6) | Cough (1), SOB (9) | Salbutamol |

AF: atrial fibrillation; AKI: acute kidney injury: CNS: central nervous system; CVS: cardiovascular system; HF: heart failure; SOB: shortness of breath

#### 4.4.3.2 Medicines associated with MRH

A total of 339 individual prescriptions were involved in 217 MRH events. In many cases, there was more than one prescribed medicine with a potential causal link to MRH. The prevalence of polypharmacy and the frequency of use of medicines with similar therapeutic outcomes e.g. ACE inhibitors, beta-blockers and diuretics will all reduce blood pressure, or similar side effect profiles e.g. morphine, agents used to treat neuropathic pain and drugs used to treat urinary incontinence may all cause constipation, made it very challenging to attribute the event to one medicine. Table 4.14 summarises the medicines involved in MRH, sub-divided into MRH due to ADR or non-adherence.

Based on the WHO-ATC classification system, medicines acting on the nervous system were most frequently involved in MRH contributing a quarter (25.1%) of all medicines causing harm, followed by those acting on the cardiovascular system (20.1%), and the alimentary tract and metabolism (18.9%). Opioids, which included morphine, oxycodone, codeine, dihydrocodeine, buprenorphine and tramadol, dominated the nervous system category. When considering ADRs only, furosemide was the most frequent causative medicine, causing 15 ADRs. This was followed by rivaroxaban (n=11), bisoprolol (n=10) and codeine (n=9). The most common causative medicine for MRH due to non-adherence was senna (n=11), followed by macrogols, furosemide and salbutamol, all of which contributed five events each.

Table 4.14 Frequency of medicines involved in MRH

| **Medicine class (number (%))** | **Medicine indication (number)** | **Causative medicine name (number)** |
|---|---|---|
| Alimentary tract and metabolism (64) (18.9%) | Acid related disorders (5) | ADR: Omeprazole (4)<br>Non-ad: Ranitidine (1) |
| | Constipation (38) | ADR: Laxatives (13), Sodium docusate (1)<br>Non-ad: Laxatives (23), Phosphate enema (2), glycerol suppositories (1) |
| | Functional GI disorders (1) | Non-ad: Metoclopramide (1) |
| | Diabetes (16) | ADR: Insulins (4), Oral hypoglycaemics (4)<br>Non-ad: Insulins (4), Oral hypoglycaemics (4) |
| | Mineral supplements (2) | ADR: Calcium and vitamin D (2) |
| Anti-infectives (30) (8.9%) | Systemic antibacterials (30) | ADR: Penicillins (14), Others (15)<br>Non-ad: Penicillins (1) |
| Blood and blood forming organs (38) (11.2%) | Iron preparations (8) | ADR: Ferrous fumarate (3), Ferrous sulphate (5) |
| | Antithrombotics (30) | ADR: Rivaroxaban (11), Dalteparin (4)<br>Aspirin (6), Clopidogrel (2), Warfarin (6)<br>Non-ad: Warfarin (1) |
| Cardiovascular system (68) (20.1%) | Antihypertensives (30) | ADR: Ramipril (8), Losartan (2), Doxazosin (1), Bisoprolol (10), Nifedipine (1), Diltiazem (2)<br>Non-ad: Ramipril (2), Bisoprolol (4) |
| | Cardiac stimulants (3) | ADR: Digoxin (2)<br>Non-ad: Midodrine (1) |
| | Vasodilators (6) | ADR: GTN spray (1), ISMN (1), Nicorandil (2)<br>Non-ad: GTN spray (1), naftidofuryl (1) |
| | Diuretics (29) | ADR: bumetanide (1), furosemide (15), spironolactone (3)<br>Non-ad: bumetanide (2), furosemide (5), metolazone (1), spironolactone (2) |
| Nervous system (85) (25.1%) | Analgesics (55) | ADR: opioids (41), ketamine (1)<br>Non-ad: opioids (9), paracetamol (4) |
| | Antiepileptics (7) | ADR: gabapentin (2), pregabalin (4)<br>Non-ad: sodium valoproate (1) |
| | Antidementia (3) | ADR: memantine (3) |
| | Antidepressants (11) | ADR: amitriptyline (3), mirtazapine (4), citalopram (2), sertraline (2) |
| | Hypnotics and anxiolytics (7) | ADR: diazepam (1), lorazepam (2), zolpidem (1), zopiclone (2)<br>Non-ad: temazepam (1) |
| | Other (2) | ADR: aripiprazole (1)<br>Non-ad: betahistine (1) |
| Respiratory system (28) (8.3%) | Obstructive airways disease (28) | ADR: Symbicort (1), Seretide (2), tiotropium (3), beclomethasone (1), theophylline (3)<br>Non-ad: Symbicort (3), Seretide (2), salbutamol (5), tiotropium (4), beclomethasone (4) |

Table 4.13 cont. Frequency of medicines involved in MRH

| Medicine class (number (%)) | Medicine indication (number) | Causative medicine name (number) |
|---|---|---|
| Others (26) (7.7%) | Anti-neoplastic and immunomodulating (6) | ADR: Pemetrexed (2), Carboplatin (4) |
| | Dermatologicals (4) | Non-ad: mometasone (2), emollients (2) |
| | Urologicals (9) | ADR: tamsulosin (4), urinary frequency (4)<br>Non-ad: tamsulosin (1) |
| | Anti-inflammatory (1) | ADR: ibuprofen (1) |
| | Systemic hormones (6) | ADR: prednisolone (4), carbimazole (1)<br>Non-ad: prednisolone (1) |

ADR: adverse drug reaction; Non-ad; non-adherence; GI: gastrointestinal

### 4.4.4 Causality assessment

All MRH events were assessed for a causal relationship between the suspected medicine(s) and event. The assessment ratings were: 44% possible, 31% probable and 24% definite (Figure 4.7). Although the majority were rated probable and definite, it is important to also consider those rated possible. In such cases, there is a link between the event and the medicine but other conditions or medicines may be implicated and so it is not possible to definitively state that a medicine was the sole cause of the event. The majority of definite events (87%) resulted in serious harm of which approximately two thirds (67%) were deemed preventable.

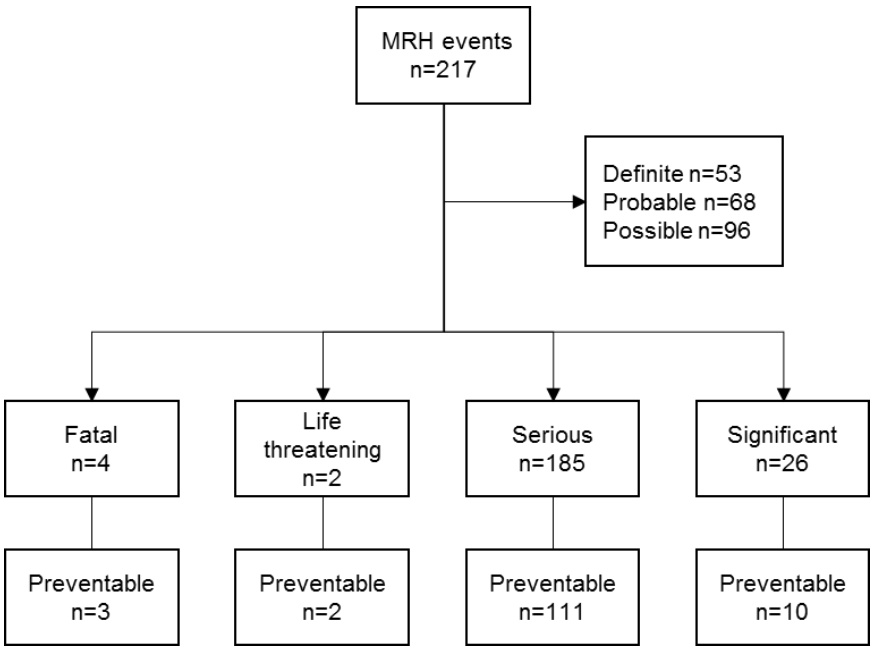
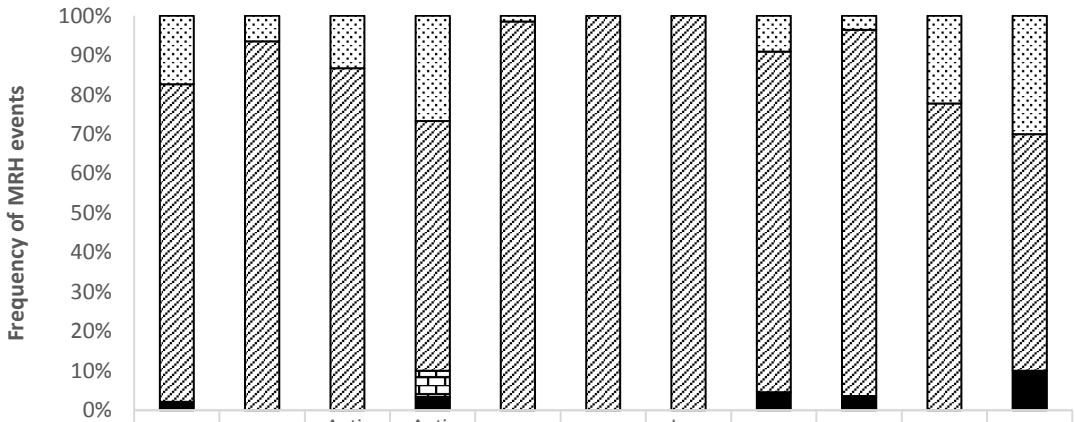



Figure 4.7 Frequency of likelihood, severity and preventability of all MRH events

### 4.4.5 Severity of MRH

Most events were categorised as serious 185 (85.3%), followed by significant 26 (12.0%), fatal 4 (1.8%) and life threatening 2 (0.9%). The four fatal MRH events were caused by both ADRs (n=3) and non-adherence (n=1).

The relationship between medicine class and severity of events is shown in Figure 4.8



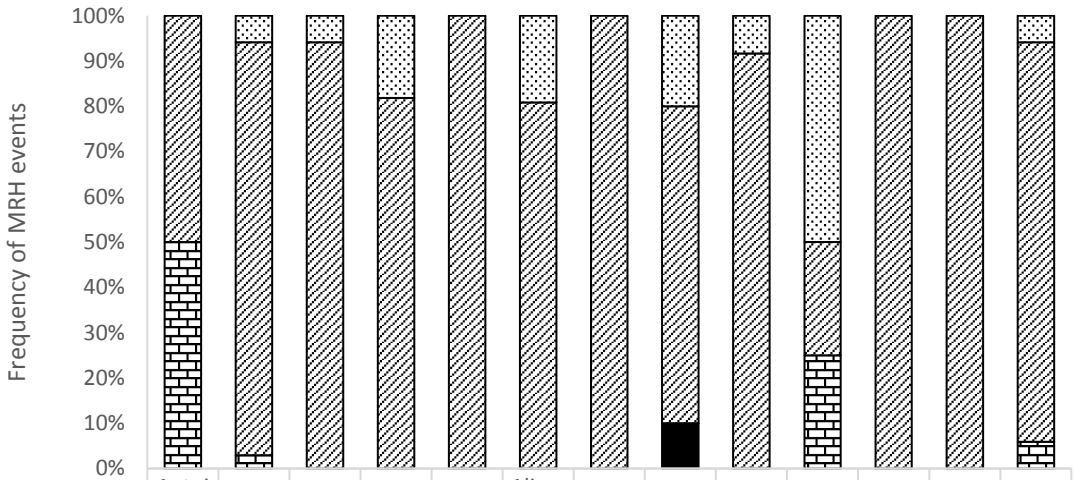

| | Alimentary | Analgesics | Anti-Infective | Anti-thrombotic | Cardiovascular | Hypoglycaemic | Iron Preparations | Psychotropic | Respiratory | Urological | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Significant | 8 | 4 | 4 | 8 | 1 | 0 | 0 | 2 | 1 | 2 | 6 |
| Serious | 37 | 58 | 26 | 19 | 67 | 16 | 8 | 19 | 26 | 7 | 12 |
| Life threat | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fatal | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 2 |

Figure 4.8 Severity of events by class of medicine

Almost all episodes of MRH attributed to cardiovascular medicines resulted in serious harm whereby an additional clinic visit or treatment alteration was required. This encapsulates the challenge presented to clinicians managing the delicate equilibrium of risk and benefit when prescribing the guideline recommended medicines for the secondary prevention of cardiovascular disease in a frail older population.

The outcome of MRH events due to antithrombotic agents is the only medicine class that spreads across all severity grades. At one end of the severity spectrum, this was attributed to the relatively minor, and expected, bleeding and bruising that are common with this class of medicines but do not require any treatment. At the other extreme, the clinical pharmacology of these medicines and the potential consequences of non-adherence can result in sub-therapeutic, or elevated drug

serum concentrations resulting in catastrophic outcomes for the patient. This is seen in the life-threatening haematological events observed where major bleeding was secondary to antithrombotic treatment, and the fatal CNS event was due to non-adherence to warfarin. This is also reflected in Figure 4.9 which illustrates the severity of MRH events by body system.



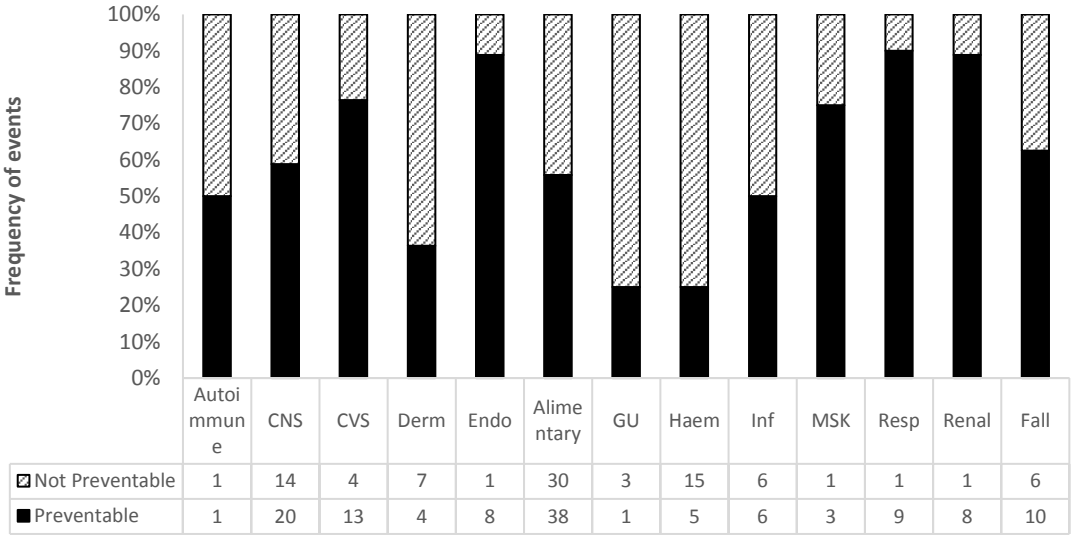

| | Autoimmune | CNS | CVS | Derm | Endo | Alimentary tract | GU | Haem | Inf | MSK | Resp | Renal | Fall |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Significant | 0 | 2 | 1 | 2 | 0 | 13 | 0 | 4 | 1 | 2 | 0 | 0 | 1 |
| Serious | 1 | 31 | 16 | 9 | 9 | 55 | 4 | 14 | 11 | 1 | 10 | 9 | 15 |
| Life threat | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Fatal | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |

Figure 4.9 Severity of MRH events by body system affected

It can also be seen from Figure 4.8 and Figure 4.9 that the high frequency of MRH events affecting the CNS and alimentary tract correspond to the common use of analgesics and those medicines used to treat conditions of the alimentary tract. In the study population, constipation was frequently reported secondary to non-adherence to laxatives or the side effect of opioids. Uncontrolled pain, confusion or dizziness were common and often due to either non-adherence to analgesics or the side effects of opioids.

### 4.4.6 Preventability

More events were considered preventable 126 (58.1%), than not preventable 90 (41.5%). It was not possible to evaluate the preventability of one event (a fall), due to conflicting information from the GP records and hospital re-admission. All events categorised as not preventable were ADRs (or ADR combined with non-adherence). This is expected as non-adherence is largely regarded as preventable.




| | Autoimmune | CNS | CVS | Derm | Endo | Alimentary | GU | Haem | Inf | MSK | Resp | Renal | Fall |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Not Preventable | 1 | 14 | 4 | 7 | 1 | 30 | 3 | 15 | 6 | 1 | 1 | 1 | 6 |
| Preventable | 1 | 20 | 13 | 4 | 8 | 38 | 1 | 5 | 6 | 3 | 9 | 8 | 10 |

Figure 4.10 Preventability of events by body system affected (n=216)

Most of the events affecting the endocrine, respiratory and renal system were considered preventable and were due to non-adherence to insulin or oral anti-diabetics; non-adherence to inhalers such as salbutamol or Seretide; and acute kidney injury secondary to furosemide. In comparison, three quarters of events affecting the haematological system were considered not preventable. Bleeding was the cause of all non-preventable haematological system MRH events. A recognised side effect of antithrombotic agents, it may be that bleeding is perceived to be an accepted consequence of prescribing such medicines and the benefit of treatment outweighs the risks.

### 4.4.7 Healthcare utilisation

There were 250 episodes of care associated with the 217 MRH events (see Table 4.15) in 158 patients, equating to 1.6 episodes of care per patient. Although most healthcare utilisation involved a visit to the GP (n=147 (58.8%)), about a third (29.6%) of all episodes of care were re-admissions to hospital.

Table 4.15 Type of healthcare utilisation due to MRH

| Healthcare type | Total (%) |
|---|---|
| GP | 147 (58.8) |
| Re-admission | 74 (29.6) |
| Out of hours | 28 (11.2) |
| A&E | 1 (0.4) |

The most severe MRH events, fatal and life-threatening, all resulted in re-admission to hospital (n=5). Serious events were managed through a range of healthcare resources; in the community (i.e. by the GP or nurse) (n=119), hospital attendance (re-admission and A&E) (n=75) or by the patient/carer themselves (n=1). This is perhaps reflective of the broad categorisation of "serious" where the main reason for allocating events to this category was a change in therapy.

#### 4.4.7.1 Re-admissions

During the 8-week follow up period there were 222 episodes of re-admission involving 156 patients (39.4%). Patients were re-admitted between one and five times, with most re-admitted once (27.8%), Table 4.16.

Table 4.16 Re-admission frequency and proportion of MRH re-admission

| Re-admission episode | Number of patients (n; %) | MRH related re-admission (n) |
|---|---|---|
| 1 | 110 (27.8) | 53 |
| 2 | 31 (7.8) | 14 |
| 3 | 12 (3.0) | 6 |
| 4 | 1 (0.2) | 1 |
| 5 | 2 (0.5) | 0 |
| Total | 156 (39.4) | 74 |

Reflecting upon national data, which uses a standard of 28-days re-admission, this re-admission rate was higher than anticipated. National data (2011-12), from the NHS Digital Indicator Portal, reports the rate of GSTFT emergency readmissions to hospital of adults aged over 75 years within 28 days of discharge as 18.23% (95% CI 17.26-19.24). This is higher than the national figure of 15.29% (95% CI 15.22-15.36%).[212] To provide a more valid comparison the proportion of patients re-admitted within 28-days was calculated as 28.5%, over 10% higher than the national data. Time to re-admission was skewed towards the first 28 days (mean time to re-admission 19.5 days [CI 95% 17.0 – 22.0 days]).

Of the 156 patients re-admitted during the 8-week follow up, 67 (43%) experienced MRH, equating to 74 MRH re-admissions and 79 events. Multiple events were experienced by four patients during a single re-admission episode; one patient experienced four MRH events and three patients experienced two events.

Table 4.17 provides a summary of MRH events where the patient was re-admitted. The likelihood, main cause (that is ADR, non-adherence or both) and preventability of the MRH event are provided. Approximately three quarters (74.3%) were preventable MRH events. All cases where non-adherence was the main cause of MRH were preventable (one episode could not be evaluated).

Table 4.17 Summary of MRH events in re-admitted patients

| **Likelihood MRH** | **Main Cause of MRH** | **Preventable MRH (n) (%)** |
|---|---|---|
| Definite (22) | ADR = 12 | 8 (66.7) |
| | Non-adherence = 6 | 6 (100.0) |
| | ADR and non-adherence = 4 | 4 (100.0) |
| Probable (25) | ADR = 19 | 10 (52.6) |
| | Non-adherence = 3 | 3 (100.0) |
| | ADR and non-adherence = 3 | 3 (100.0) |
| Possible (32) | ADR = 21 | 12 (57.1) |
| | Non-adherence = 8 | 7 (87.5)* |
| | ADR and non-adherence = 3 | 2 (66.7) |

*unable to evaluate preventability in 1 case

## 4.5 Discussion

This study has shown that approximately two in every five frail older patients discharged from hospital following an episode of acute care will experience MRH and more than half of these events are preventable. Treatment modification was required in the majority of cases (88%) as signified by a severity rating of serious or above. Given the reported preventability of MRH in this study (58.1% of MRH were deemed preventable), these results suggest that there is a significant level of avoidable healthcare expenditure due to MRH. Indeed, hospital admission, the most costly type of healthcare utilisation, accounted for approximately one third of care episodes associated with MRH.

### 4.5.1 MRH incidence in a frail population

The study population was drawn from the OPU at St. Thomas' Hospital where admission to the unit is based on bed availability and patient need. The criteria used to assess need intentionally selects the most vulnerable patients and so it is unsurprising that the patient demographics described the majority of the study population as aged over 80 years old and multimorbid with high levels of dependence. Considering hand grip in isolation would suggest that the study population is sarcopenic, and may be frail. A degree of caution should be applied when interpreting these results. Hand grip strength can be influenced by cognitive impairment limiting an individual's ability to follow instructions or conditions such as rheumatoid arthritis compromising physical ability. Cognitive impairment was not widespread in the study population however connective tissue disorder, which includes rheumatoid arthritis, was present in almost a third of the cohort. Overall, the demographics reflect a group of complex older adults who are frequently excluded from clinical trials and so there is a paucity of evidence to support the risk versus benefit judgements that are required when prescribing medicines.

Harm from medicines in older adults however is extensively reported, with significant variability in incidence, 6.5-39%, due to heterogeneity in populations, outcome definitions and study design, as outlined in Chapter 1 and Chapter 3. Much of the published research has focussed upon identifying older adults at greatest risk of inpatient ADRs/ADEs but few have explored harm post-discharge[11,24] in frail older populations. The incidence of post-discharge MRH ranges from 18.4-37.5%.[24] Gray and colleagues[25] reported a 20% post-discharge ADE incidence in older patients

receiving home health services. Home health is an agency based system which provides multi-disciplinary services based on patient needs following hospital discharge. Patients are likely to be housebound, have functional limitations and take several medicines; that is, they are likely to be frail. The reported ADE rate is less than identified in this study and whilst study demographics appear comparable, several groups of patients were excluded from the Gray study including, those who had suffered a thrombotic event in the previous 2 months, dementia patients with no carer and those who had a delay between discharge and initiation of the home health service. These excluded patients are likely to be the most at risk of MRH for several reasons. For example, patients who have suffered a recent thrombotic event are normally initiated on antithrombotic therapy, a group of medicines which were frequently associated with MRH in this, and other[88] studies. Their physiological reserve is likely to be reduced and their psychosocial resilience diminished after the acute insult. Considering the conceptual framework outlined earlier, deficits across multiple areas (for example levels of independence, mood) in combination with exposure to a high-risk medicine will increase the likelihood of experiencing MRH.

With few exclusion criteria, and recruitment from the OPU, the study population is likely to represent a highly vulnerable group of older patients. Similar to the home health service, community based support teams are deployed across the GSTFT localities with the aim of admission avoidance. Should a patient present to hospital, a service embedded within the emergency department screens for "frailty at the front door"[213,214] to ensure that an accurate problems list is created and appropriate actions taken, which often results in the avoidance of unnecessary admissions. Patients who are admitted to GSTFT are therefore potentially more unwell than those recruited in other studies. In these patients a small insult may overwhelm already depleted physiological and psychosocial reserves so that admission is required to provide the level of care needed. This elevated level of vulnerability may also explain the higher MRH rate reported in this study and the high re-admission rate. Most re-admissions occurred within the first week of discharge which is consistent with other ADR studies[26]. This is also consistent with the slow time to recovery witnessed in frail older adults after an acute insult[150] such as a hospital admission, and so they are more vulnerable during the post-discharge period. Few studies have focussed on this high-risk stage of the patient journey[215], and none have included such a frail UK population.

### 4.5.2 Assessment of MRH in a frail population

#### 4.5.2.1 Data sources

Identifying and confirming MRH in a complex older population is challenging and the methods employed in the identification, classification and confirmation of MRH in this study must be considered when comparing the incidence rates. Often presenting with atypical symptoms or geriatric syndromes, on a background of multiple comorbidities and polypharmacy, it can sometimes be impossible to disentangle the causal pathways. Unique in its approach, this study used up to three data sources to confirm MRH: GP records, patient interview and re-admission review, allowing every patient to be followed up and a detailed case history to be constructed, reviewed and associations agreed. This method also resulted in no loss to follow up and enabled more robust identification of MRH in a complex population, and so may partly explain the higher incidence. Furthermore, many studies investigating MRH are limited as they regularly use existing databases or clinical records to retrospectively identify events[18,33], or use only a single source for follow up[25,26]. Often, they are reliant upon a clinician for the accurate identification of MRH, attribution of harm to specific medicines and documentation in the patient's records. It is recognised that clinicians may fail to identify clinical presentations due to ADRs and, in some instances, rather than remove the culprit medicine, a new medicine is prescribed to treat the side effects. Known as the prescribing cascade[216] this results in polypharmacy, which adds to the complexity of identifying MRH.

#### 4.5.2.2 Causality assessment

The use of algorithms to assign causality to a specific medicine is common practice in ADR studies[18,25,85], although such approaches have limitations, especially when applied to an older, medically complex population. To mitigate against these limitations, in this study, the Naranjo algorithm[129] was used as a guide as scores would have been influenced by the inability to re-challenge a suspect ADR (one of the Naranjo assessment criteria) and almost all patients had a potential "other cause" that could have led to the reaction.

Given the demographics of the study population and the aforementioned difficulty in identifying true causality, it is not surprising that in this study only a quarter of all MRH events were classed as definite. This result is comparable to Tangiisuran[85], who conducted a prospective study of

inpatient ADRs in an older population, but is much higher than other post-discharge MRH studies where between 3-6% of events were considered definite[25,26]. The method of follow up employed contributes significantly to the difference seen. Patient self-reporting via telephone interview was the only source of follow up used in the previous post-discharge studies compared to multiple sources, including patients and clinicians, in this study. Patients may fail to recognise symptoms as MRH or not report relatively minor side effects considering them to be an expected consequence of taking medicines. Tangiisuran's study took place in the inpatient setting where clinicians could be consulted at the time of the event and there was greater access to clinical investigations, allowing more confidence in the final confirmation of ADR.

The complexity of such presentations emphasises the need to consider not only the definite events but also the probable and possible categories, which is common practice in research of this nature.[18,25,85] In doing so, the risk of event misclassification and the potential impact of this when investigating statistical associations between risk variables and MRH needs to be acknowledged. In an attempt to limit such misclassifications and ensure consistency in categorisation of harm, this study applied a multiple stage review process where every case was reviewed by both the research pharmacist and a senior clinical academic.

Overall, the incidence of MRH was higher than previously reported which may be explained by the level of frailty of the study population, the extended outcome definition to incorporate non-adherence and the robust follow up method. This result is consistent with the theory proposed in the conceptual framework that heightened vulnerability increases the likelihood of MRH. The method employed is reflective of the challenges in assigning causality which is frequently multifactorial.

### 4.5.3 Medicines involved in MRH

Medicines acting on the nervous system were most frequently involved in MRH contributing to a quarter (25.1%) of all medicines causing harm, followed by those acting on the cardiovascular system (20.1%), and the alimentary tract and metabolism (18.9%). As these were the three most commonly prescribed groups of medicines, the frequency of harm may reflect the frequency of exposure. However, medicines acting on the nervous and cardiovascular systems are recurrently reported in the literature as causing ADRs and ADEs in older adults.[25,85,88] This may be due to

altered pharmacodynamics in older populations increasing their susceptibility to the adverse effects of agents acting on the nervous system. With regard to cardiovascular agents, often multiple medicines with similar side effect profiles are prescribed, for example antihypertensives, and so the propensity for harm is increased. Furthermore, these medicines may interact with pre-existing geriatric syndromes, such as falls. Medicines acting on the alimentary tract and metabolism, was dominated by laxatives but also included medicines used in the management of diabetes which are also commonly reported as causing harm in older adults[85]. Although MRH resulting from the use of laxatives is less well reported, the high incidence of harm associated with these medicines in this study is probably due to the definition of MRH used, which included harm due to failure to receive a medicine. Most of the reported harm relating to laxatives was constipation secondary to non-adherence, either alone or in conjunction with an ADR from another prescribed medicine e.g. codeine.

Reflecting on the medicines most frequently involved in MRH (those acting on the nervous system, cardiovascular system and alimentary tract), it is unsurprising that the alimentary tract and nervous systems were the most commonly affected body systems. This is consistent with other studies investigating both inpatient and outpatient ADEs/ADRs in older adults[18,25,85,88]. Constipation and falls accounted for a fifth of all MRH in this study, conditions that are considered geriatric syndromes and are known to affect many frail older adults. As a consequence, it was sometimes challenging to definitively discriminate between whether the clinical presentation of a fall or constipation was the manifestation of frailty or due to MRH. In the majority of cases the medicine probably augmented an underlying vulnerability.

### 4.5.4 Defining harm from medicines in a frail older population

It was important for this study to consider a wider definition of MRH as many previous studies have concentrated on ADRs alone. Although potentially easier to measure using an algorithm based approach, ADRs are only one of the medication related problems experienced by older adults at discharge. Over the past 50 years adherence to long term therapies has remained at around 50%[65] and is associated with poor health outcomes. In the USA, 33-69% of all medicine related hospital admissions are due to poor adherence to treatment.[66] Often not considered as a potential cause of the clinical presentation, it is important to investigate this arguably avoidable

source of MRH. As demonstrated in the current study, the medicine not being available to the patient was a problem, as the harm experienced by around a third of patients was associated, at least in part, with not receiving their prescribed medicines. Non-adherence in older adults is often thought to be unintentional: forgetting due to poor memory, or difficulty in opening packets due to impaired manual dexterity. It is however more complicated and research highlights that approximately 50% of non-adherence in older adults is intentional.[71] Six factors influencing adherence to therapy have been proposed by Mukhtar and colleagues, based on Leventhal's Common-Sense Model of Self-Regulation. These are: illness beliefs, perceived risks (e.g. adverse effects), benefits and necessity of treatments, the patient-practitioner relationship, inter-current physical and mental illness, financial constraints and pharmaceutical/pharmacological issues (polypharmacy/regimen complexity).[69] The potential interplay between physiological and psychosocial systems and the consequential action of the patient, as described in the conceptual framework proposed earlier, is evident in these factors.

### 4.5.5 The influence of polypharmacy

Polypharmacy was common in the study population where the mean number of medicines on admission was almost nine, increasing to ten at discharge. This finding is consistent with previous research where it was found that 62.1% of the study sample had at least one or more additional medicines at discharge.[217] Due to the ubiquity of polypharmacy in the study cohort it was not always possible to attribute MRH to a single medicine e.g. constipation in a patient prescribed oxycodone, ferrous sulphate, solifenacin, senna and macrogol but is non-adherent to the laxatives. This highlights one of the challenges when conducting research in this area where patient presentation is often complex and requires a different approach to that of the traditional "single body system", guideline driven, medicine. Undeniably, however, guideline based prescribing can result in significant polypharmacy and exposes a patient to the risk of drug-drug interactions[218,219] and is the most consistently reported single predictor of MRH.

Over recent years, polypharmacy has attracted growing interest, as highlighted by two recent publications: King's Fund Polypharmacy and Medicines Optimisation document[52] and the Scottish Polypharmacy Guidance[54]. Both suggest targeting frail older patients for medicines reviews, recognising the excessive harm that can result through the use of inappropriate medicines in this

population. Similar to the NICE multimorbidity guidelines[220], the Scottish Polypharmacy Guidance offers pragmatic guidance on the process of medicines reviews, proposing seven steps which focus on the: 1. Aims; 2. Need; 3. Effectiveness; 4. Safety; 5. Cost effectiveness and; 6. Adherence/Patient centeredness of the medicines. The impact of conducting such medicine reviews on the incidence of MRH and which patients would benefit most requires further investigation.

### 4.5.6 Healthcare utilisation

The healthcare utilisation resulting from MRH ranged from accessing the out of hours services to admission to hospital, although the most common resource used was the GP, with 147 (58.8%) consultations relating to MRH. Healthcare utilisation was closely linked to the severity of MRH reported where serious events accounted for 85.3% of all MRH and, by definition, required treatment modification and so access to healthcare. Few studies have investigated this aspect as most focus on re-admission only and report a re-admission rate between 40-64%[32,33,221] over a wide-ranging follow up period of between 60-365 days from discharge. A comparison of this current study with the study by Thomas[32], who followed patients for 60 days after discharge, would seem the most valid as patients re-admitted 1 year after discharge are likely to represent a different population. Thomas and colleagues reviewed MRH in a discharge cohort of 100 patients, representing a convenience sample from 1611 patients recruited to another study. Patients were followed for 60 days after discharge and MRH, using the definition of DRP (including problems associated with adverse events, treatment effectiveness and treatment cost), was seen in 64% of patients. Whilst this is higher than the incidence reported in this current study (29.6%) it can be explained by a number of crucial differences in study design. The outcome definition used, DRP, is likely to report a high incidence of MRH due to its wide scope, patients followed were not clearly defined and were generally much younger than those seen in the GSTFT population, with a mean age of 56 years compared to 84 years old respectively. Re-admission in our study population was higher than national data reports for GSTFT and will be explored in more detail in the next chapter.

### 4.5.7 Limitations

The generalisability of our findings to the general older population, often defined as >65 years old, may be limited as the study participants represented the frail oldest old. Comparison with other studies to help assess generalisability of the findings was difficult as so few post-discharge MRH studies have been conducted and different definitions for outcome, preventability, severity are frequently used, if reported at all. Considering severity for example, Forster and colleagues[222], used a self-derived scale consisting of 6 categories: serious laboratory abnormality only; one day of symptoms; several days of symptoms; non-permanent disability, or death. 94% of patients suffered non-permanent disability or more than one day of symptoms in a study of post-discharge adverse events. There were no deaths but permanent disability occurred in 3% of the population. Abnormal laboratory results and 1 day of symptoms affected 4%. Four fatalities were reported in this study which may reflect the level of frailty within the study population where a relatively minor insult can have disproportionate consequences.

A relatively small number of patients were screened and subsequently recruited to the study in comparison to the total number of patients discharged from the unit. Screening and recruitment were limited by manpower and access to patients. The extensive follow up process, including review of re-admissions, patient phone calls and visits to GP surgeries were highly labour intensive, but provided a robust approach to MRH identification and categorisation. The re-admission of patients frequently diverted research staff from recruiting patients, as a result, the study population may not be representative of the OPU population in general as reflected in the demographics where a greater proportion of white females were recruited to the study than were discharge from the unit during the same time period. This may be due to non-white patients being unable to speak English, requiring an interpreter for recruitment.

Further recruitment bias may be suspected when considering the mean depression and anxiety scores. These suggest low levels of anxiety and depression in the study population which is inconsistent with the reported prevalence of these conditions in the older population.[223] Recruitment bias is likely to have contributed to this as they represent a group which can be hard to recruit.[224]

Confirmation and classification of the final outcomes were conducted by members of the research team (the EPC) who were not blinded to the study aim and therefore bias may have been

introduced. In the case of re-admissions, clinicians independent of the study group assigned causality, severity and preventability to the event alongside the principal researcher. This approach is likely to reduce any bias and, although data were not collected at the time, very few case outcomes were significantly changed when reviewed by the EPC. Most changes to classification were in relation to the classification of likelihood, for example from possible to probable and *vice versa*, to align with the study definition. As already discussed, the assignment of causality in this population is challenging and all definite, probable and possible events were classified as MRH therefore the impact of any bias on the results is likely to be minimal.

Healthcare utilisation was not a measure of MRH causing healthcare utilisation, but a measure of the number of care episodes that were associated with MRH. That is, a patient may have presented for another reason and MRH was subsequently identified but was not the cause of the presentation. It is therefore not possible to conclude that all these episodes of care were additional, although are likely to be directly attributable to the episode of MRH. In future, it would be helpful to categorise patients based on healthcare utilisation due to MRH, although in this complex population it is common for more than one event to lead to a presentation and so this may be challenging.

## 4.6 Conclusion

The incidence of MRH in this study was higher than previously reported. Study definitions and design are likely to have contributed to some of this variation however the study population is unique and is likely to be the main cause. The patients in this study represent a complex frail older population who are at high-risk of experiencing adverse outcomes. This supports the theory proposed in the conceptual framework in Chapter 3 (Figure 3.3) that, similar to frailty, multiple deficits across physiological and psychological systems results in a disproportionate level of harm when exposed to an insult. In this study, the insult is in the form of a medicine. This theory and the statistical significance of associations between physiological and psychosocial variables and post discharge MRH will be explored in the next chapter.

# Chapter 5 Exploration of variables associated with MRH

## 5.1 Introduction

As identified from the broader literature (Chapter 1), and confirmed in the systematic review (Chapter 3), previous studies investigating MRH in older adults have focussed on the influence that comorbidities and medicine related variables have on the risk of experiencing MRH. Few studies have considered the impact of psychological and social variables. The conceptual framework outlined in Chapter 3 (Figure 3.3) describes the important contribution that such variables could make when identifying frail patients. The framework highlighted the similarities between frailty, geriatric syndromes and MRH, namely that they are multifactorial in nature with multiple causal pathways. Given these commonalities, and the limited research exploring the influence of psychosocial variables on MRH, further study of this area is warranted and will be presented in this chapter.

Around 40% (n=156) of patients in this study were re-admitted during the 8-week follow up period, with approximately half of these re-admissions (47%) being potentially related to MRH. Almost three quarters (74.3%) of the MRH re-admissions were considered preventable. Re-admission is the costliest outcome of MRH, with penalties levied on the hospitals when they occur within 28-days of discharge. The ability to identify those at greatest risk of MRH re-admission, to target interventions, would therefore allow a more efficient delivery of healthcare as well as the avoidance of distress by the patient. Nair and colleagues developed a model to predict the risk of admission due to MRH in community based patients. The model had only modest performance, as described in more detail in Chapter 3, and didn't consider psychosocial variables. Furthermore, risk factors for re-admission may be different to those associated with admission due to the increased vulnerability in the immediate post-discharge period[23]. To better understand the variables that predict MRH re-admission, this chapter will further explore the associations between selected variables and MRH re-admission.

## 5.2 Aim and objectives

This chapter aims to explore the relationships between physiological and psychosocial variables and the risk of post-discharge MRH. It will do so by addressing the following objectives:

1. Measure and compare the associations of variables studied in previous MRH prediction model research with MRH in this study population.
2. Explore the relationship between re-admission with MRH and physiological and psychosocial variables.
3. Explore the potential of frailty indicators, proposed for use in the acute care setting, to improve prediction of MRH re-admission.

## 5.3 Methods

The dataset described in Chapter 4 was further interrogated with the aim of identifying relationships between MRH and selected variables. Full methods detailing the data collection, identification and classification of MRH are described in Chapter 4, a summary of which is provided below.

Three distinct analyses were conducted:

1. A comparison of patients who experienced MRH to those who did not through exploration of the relationships between independent variables and MRH using binary logistic regression. In the discussion section of this chapter, the results from this analysis are compared with variables reported in the studies identified in the systematic review (see Chapter 3)
2. Survival analysis with the identification of variables associated with MRH re-admission
3. A comparison of patients re-admitted with and without MRH.

The methods used for each analysis, including the process of selecting variables for analysis, are outlined below.

### 5.3.1 Summary of prospective cohort study methods

Patients discharged from the OPU at GSTFT over 24 consecutive months were invited to participate in the study. Data were collected prospectively and is summarised in three key stages: 1. baseline data collection, including demographic, clinical, medicines and social data; 2. follow-up data collection, where any MRH associated healthcare utilisation was identified; 3. confirmation and classification of MRH, where causality, likelihood, preventability and severity were confirmed. Full details are described in the methods section of Chapter 4.

### 5.3.2 Variable selection

There is no defined method for the selection of variables for exploratory analysis. Previous studies have utilised data-driven techniques[68] however they have failed to develop risk prediction models with adequate accuracy for use in clinical practice. Therefore, variables considered for this analysis were derived from the literature and refined by expert consideration (the supervisory team).

The studies identified by the systematic review were revisited in order to identify potential variables for further analysis in this study population. These studies identified a large number of variables, mainly focussing on clinical and medicine related factors. Between nine and sixty seven variables were reported, with Nair[68] reporting the most and Trivalle[88] the least. Across these studies several common variables were associated with MRH following univariate analysis, however there were also many where the association with MRH was inconclusive, or no link was found. Examples of the variables for each of these groups is provided in Table 5.1. Due to this variance, statistical significance from any single dataset alone could not be used to select suitable variables for further study. Variables were therefore selected, following discussion by the supervisory team, based upon their face validity and repeated occurrence across the systematic review studies. The selection processes deliberately included variables from a range of groupings (patient characteristics, comorbidities, clinical, social and medicines) and with varying consistency of association as outlined in Table 5.1. The variables included for example age, gender, ethnicity, CCI, eGFR, length of stay ≥12 days, albumin <35g/l, Barthel Index, number of medicines and the use of an MCA.

Table 5.1 Summary of the relationship between selected variables and MRH following univariate analysis (using chi square analysis) as reported by previous MRH risk prediction model studies

| | Variable | Significance (p) | | | |
|---|---|---|---|---|---|
| | | **Tangiisuran**[85] | **Onder**[18] | **Trivalle**[88] | **Nair**[68] |
| **Consistent association** | No. of medicines | <0.001[$] | <0.001 | <0.001^ | 0.05[◦] |
| | Antihypertensives | 0.002 | - | 0.01 | <0.001 |
| | eGFR <60ml/min | - | 0.02 | - | <0.001 |
| **Inconsistent association** | No. of comorbidities | 0.308* | <0.001* | 0.03 | 0.01[#] |
| | Heart failure | 0.852 | <0.001 | - | 0.04 |
| | Previous ADR | 0.598 | <0.001 | - | 0.57 |
| **Not associated** | Age | 0.62 | 0.15[¥] | - | 0.07[†] |
| | Gender | 0.855 | - | No value given | 0.42 |
| | ADL disability | No value given | 0.12 | - | 0.22 |

ADL: activities of daily living; ADR: adverse drug reaction: eGFR: estimated glomerular filtration rate; [$] ≥8 medicines; ^ at multivariate level; [◦] ≥9 medicines; - not reported/measured in study; * ≥4 co-morbidities; [#]≥7 co-morbidities; [¥]≥80 years; [†]≥85 years

An important aspect of this exploratory analysis was to investigate the influence of psychosocial variables on the likelihood of MRH. In the conceptual framework proposed in Chapter 3 (Figure 3.3) similarities between the cumulative deficits model of frailty (or FI)[154] and MRH were described, whereby physiological, psychological and social variables were thought to contribute to the likelihood of an individual experiencing an adverse outcome. Therefore, a review of the FI literature was conducted in order to facilitate the selection of psychosocial variables for analysis.

Requiring data for a minimum of 30 variables, the practical feasibility of the FI in the acute care setting has been questioned. The need for an operationalised measure of frailty in the acute care setting was recognised by Soong and colleagues who recently derived a set of frailty indicators appropriate for use in the acute care setting.[225] They conducted a literature review to identify studies that developed or validated frailty assessments in the acute care setting. From the review, 31 indicators were identified and were grouped into five categories: social demographics, phenotype model, high intensity service usage, accumulated deficits model and bio-gerontological model. As described by Soong, these indicators were reviewed over two rounds, by an expert panel using a modified Delphi technique. Expert panel members were selected

nationally on the basis that they were research-active, or providing frailty care, or were involved in charities associated with frailty. The panel consisted of physicians (Consultant Geriatricians and Psychiatrists and, GPs), nurses, pharmacists, physiotherapists, dieticians, psychologists, social care managers (a Chief Executive of social care, and a care home manager), academics and specialists from the charity sector. They were asked to rate the 31 variables, using a five point Likert Scale ranging from "not useful at all" to "very useful". Using a cut-off 80% agreement ("useful or "very useful") for inclusion in the final list resulted in the selection of 12 frailty indicators (see Table 5.2). The variables agreed by the consensus panel focused largely on accumulated deficits and high intensity service usage. The authors recognised that whilst these may not fully reflect the current definitions of frailty, they cover a range of physiological and psychosocial variables, and are potentially indicative of variables that are easily accessible and useful in the acute care setting. Therefore, where the data were available, these variables were incorporated into the analysis in this study. Data pertaining to pressure ulcer risk and multiple hospital admission episodes was not available in the study dataset. The measure used for each variable is outlined in Table 5.2, with greater detail provided in the methods section of Chapter 4.

Table 5.2 Recognised frailty indicators and the measurement used in the current study

| **Frailty variable** | **Measure used (current study)** | **Classification** | **% agreement (n=41)** |
|---|---|---|---|
| Falls | >1 (12 months) | Accumulated deficits | 95.1 (39) |
| Impaired cognition | AMTS <8 | Accumulated deficits | 95.1 (39) |
| Nutritional status | MUST ≥1 | Accumulated deficits | 92.7 (38) |
| Functional dependence | Barthel | Accumulated deficits | 90.2 (37) |
| Multiple morbidity | CCI | Accumulated deficits | 90.2 (37) |
| Impaired mobility | Barthel | Accumulated deficits | 87.8 (36) |
| Multiple hospital admissions | Unavailable | High intensity service use | 87.8 (36) |
| Large package of care at home | ≥4 visits/day | High intensity service use | 85.4 (35) |
| Care home resident | Yes/no | High intensity service use | 82.9 (34) |
| Polypharmacy | No. of discharge medicines | Accumulated deficits | 82.9 (34) |
| Incontinence | Barthel (bowel and bladder) | Accumulated deficits | 80.5 (33) |
| Pressure ulcer risk | Unavailable | Accumulated deficits | 80.5 (33) |

Adapted from Soong et. al[225]

AMTS: abbreviated mental test score; MUST: malnutritional universal screening tool; CCI: Charlson comorbidity index

In addition, hand grip was included in the variables selected for my analysis. Including this variable allowed further exploration of the relationship between markers of frailty and MRH. This is because it is a quick and reproducible measure of sarcopenia[184], which is often present in frail older adults, and a component of the phenotype model of frailty[151].

### 5.3.3 Comparison of patients with MRH and without

To further understand the factors that influence MRH in the study population, binary logistic regression was applied to the dataset. A commonly used statistical method in prognostic research, binary logistic regression facilitates the identification of statistically significant associations between the outcome of interest and the independent variable(s).[109] The associations were compared with selected variables explored in the studies identified by the systematic review.

### 5.3.4 Survival analysis with the identification of variables associated with MRH re-admission

MRH re-admission was defined as those who were re-admitted with MRH during their 8-week follow up period. Survival analysis was used to explore the relationship between physiological and psychosocial variables and MRH re-admission, with the time to event measure being the time elapsed between the date of discharge to the date of hospital re-admission.

#### 5.3.4.1 Survival analysis

Previous risk prediction model studies have failed to consider that by the end of the study period many patients will not have experienced MRH, however this does not mean that they would not go on to experience MRH. They also do not consider competing events e.g. a patient dying during the study period. In this study, 60% of the population did not experience MRH, and around 10% (n=37) died during the study follow up period. Survival analysis allows such events to be taken into account through a process known as censoring, and so improves the reliability of any conclusions drawn from the data. Survival analysis was therefore used to identify variables associated with MRH re-admission, compared to no MRH occurring.

Patients who experienced a fall were allocated to one of two groups; those experiencing up to 1 fall and those with more than 1 fall in the preceding 12 months, based on the distinction used in clinical practice that a patient who has more than one fall in 12 months is in need of a detailed assessment.[226] Based upon accepted clinical measures, an AMTS of <8 was used to define cognitive impairment.[177] After discussion with the lead Geriatrician for the Department of Ageing and Health at GSTFT, the package of care was categorised as a light care package, a heavy care package or institutional care. A light care package was defined as 0-3 visits a day, a heavy care package was four or more visits a day and included 24-hour home care, and institutional care was 24-hour care within a nursing or residential home or bed based rehabilitation units. The definitions of the other variables investigated are described in detail in Chapter 4.

#### 5.3.4.2 Comparison of those re-admitted with MRH and those re-admitted without MRH

It is recognised that the previous analyses comparing those re-admitted with MRH and those not re-admitted may have identified variables that are predictive of re-admission in general, rather than re-admission with MRH. Therefore, a comparison of those re-admitted with MRH and those re-admitted without MRH was conducted with a focus on the variables identified by Soong and colleagues[225]

#### 5.3.4.3 Healthcare utilisation secondary to serious MRH

As outlined in Chapter 3 (Figure 3.5), the same MRH may result in various levels of healthcare utilisation in different individuals. In this thesis, it has been proposed that this is due to variations in physiological and psychosocial reserve. Case examples, drawn from the dataset described in Chapter 4, are used to illustrate this hypothesis.

### 5.3.5 Analysis

Statistics were applied to describe population characteristics, the frequency of MRH re-admission and to identify differences between those who experienced MRH and those who did not. Categorical data were presented as numbers (%) and numeric data were presented as a mean (SD). Non-normally distributed numeric data were presented as median (inter-quartile range).

Binary logistic regression was used to assess the risk of MRH in relation to a particular independent variable for all study patients, and for the sub-analysis of all re-admitted patients.

The relationships between independent variables and MRH re-admission were identified using survival analysis. Kaplan-Meier was conducted for categorical data, with the difference between two groups assessed using the logrank test. Kaplan-Meier plots were presented with the corresponding p-value for the logrank test to determine significance. Cox regression models were used for continuous data, and the results were reported as hazard ratios with the corresponding 95% confidence intervals and p values. Variables significantly associated with MRH re-admission ($p<0.05$) were entered into a Cox regression model to assess for multicollinearity.

The analysis was performed using SPSS software (version 24.0; SPSS, Inc., Chicago, IL, USA).

## 5.4 Results

### 5.4.1 Comparison of patients with MRH and without

The characteristics of those patients who experienced MRH and those who did not are presented in Table 5.3. Univariate analysis comparing the two groups revealed a number of variables significantly associated with MRH (set at an *a* priori of p=0.05) (Table 5.4).

The two groups were well matched for gender, age, ethnicity and a range of clinical, medicine related and functional variables (Table 5.3). Almost all study participants were probably frail based on the measurement of hand grip strength alone, using the recognised cut offs (male <30kg; female <20kg)[184], and therefore comparison of frail and non-frail was not possible. However, when analysed on a continuous scale, lower hand grip strength (men only) was associated with an increased risk of MRH. Patients who experienced MRH were also prescribed significantly more medicines on discharge (mean number of medicines: MRH 11.2 (SD 4.3), no MRH 9.3 (SD 4.3). A MUST score equal to one was also significantly associated with MRH. Patients who experienced MRH were more likely to live alone (69% vs 58.2%) but this difference was not statistically significant (OR 1.28 [95% CI 0.83-1.37]).

Table 5.3 Comparison of patient characteristics in patients with MRH and without

| Characteristic | Number of patients (%) | | |
|---|---|---|---|
| | MRH (n=158) | No MRH (n=238) | Total (n=396) |
| **Demographics** | | | |
| Gender (female) | 109 (69) | 147 (62) | 256 (65) |
| Age (years)^ | 84 (6.7) | 83 (7.2) | 83 (7.0) |
| Ethnicity (white) | 143 (91) | 209 (88) | 352 (89) |
| **Clinical** | | | |
| CCI^ | 2.3 (1.6) | 2.1 (1.7) | 2.1 (1.6) |
| eGFR (ml/min/1.73m$^2$)˜ | 53 (31-79) | 60 (37-80) | 57 (35-79) |
| Length of stay˜ | 11 (7-18) | 10 (6-16) | 10 (6-17) |
| Died | 12 (7.6) | 25 (10.6) | 37 (9.3) |
| AMTS^ (range 0-10) | 8.5 (1.6) | 8.2 (1.8) | 8.3 (1.7) |
| MUST† | | | |
| 0 | 77 (49) | 132 (59) | 209 (55) |
| 1 | 38 (25) | 34 (16)* | 72 (19) |
| 2 | 40 (26) | 59 (26) | 99 (26) |
| **Comorbidities** | | | |
| Hypertension | 103 (65) | 140 (59) | 243 (61) |
| Connective tissue disease | 46 (29) | 72 (30) | 118 (30) |
| Diabetes | 50 (32) | 58 (24) | 108 (27) |
| Atrial fibrillation | 49 (31) | 55 (23) | 104 (26) |
| Hyperlipidaemia | 34 (22) | 56 (24) | 90 (23) |
| IHD | 23 (15) | 33 (14) | 56 (14) |
| Anaemia | 21 (13) | 20 (8) | 41 (10) |
| **Medicine related** | | | |
| No. admission medicines^ | 9.3 (4.2) | 8.4 (4.5) | 8.8 (4.4) |
| No. discharge medicines^ | 11.2 (4.3) | 9.3 (4.3)* | 10.1 (4.4) |
| Previous ADR | 45 (28.5) | 57 (24.0) | 102 (25.8) |
| MCA† | 68 (49.6) | 104 (43.7) | 172 (45.9) |
| Regular pharmacist† | 156 (99.4) | 234 (98.3) | 390 (98.7) |
| **Frailty measures** | | | |
| Hand Grip^ | | | |
| Female (kg)† | 12.8 (5.8) | 11.8 (5.8) | 12.2 (5.8) |
| Male (kg) | 17.7 (8.5) | 21.2 (6.3)* | 19.9 (7.3) |
| Falls (>1 in 12months)† | 71 (45.2) | 114 (47.9) | 185 (46.8) |
| **Dependency in ADLs** | | | |
| Barthel Index^ (range 0-20) | 13.0 (4.8) | 13.4 (4.4) | 13.2 (4.6) |
| **Social circumstances** | | | |
| Lives alone | 109 (69.0) | 138 (58.2) | 247 (62.5) |

^ Mean (SD); ˜ Median (IQR); † missing data: MUST n=380, MCA n=395, community pharmacist n=395, hand grip n=254, falls n=395; *p<0.05

ADLs: activities of daily living; ADR: adverse drug reaction; AMTS: abbreviated mental test score; CCI: Charlson comorbidity index; eGFR: estimated glomerular filtration rate; IHD: ischaemic heart disease; MCA: multi-compartment compliance aid; MUST: malnutrition universal screening tool

Table 5.4 Univariate analysis of potential predictor variables for MRH (based on binary logistic regression)

| Variables | | Odds ratio (95% CI) | p |
|---|---|---|---|
| **Demographics** | | | |
| Gender (female) | | 1.38 (0.90 – 2.11) | 0.14 |
| Age | | 1.03 (1.00 – 1.06) | 0.08 |
| Ethnicity | | | |
| White | | 1.00 | |
| Non-white | | 0.76 (0.39 – 1.46) | 0.41 |
| **Clinical** | | | |
| CCI | | 1.06 (0.94 – 1.20) | 0.35 |
| eGFR (ml/min/1.73m$^2$) | | 0.995 (0.99 – 1.00) | 0.07 |
| Length of stay ≥ 12 days | | 1.27 (0.85 – 1.91) | 0.25 |
| Albumin <35g/l | | 1.02 (0.63 – 1.68) | 0.92 |
| AMTS | | 1.11 (0.98 – 1.25) | 0.10 |
| MUST: | 0 | 1.00 | |
| | 1 | 1.92 (1.12 – 3.29) | 0.02 |
| | 2 | 1.16 (0.71 – 1.90) | 0.55 |
| **Co-morbidities** | | | |
| Atrial fibrillation | | 1.50 (0.95 – 2.35) | 0.08 |
| CCF | | 1.26 (0.74 – 2.16) | 0.40 |
| Diabetes | | 1.44 (0.92 – 2.25) | 0.11 |
| Hypertension | | 1.31 (0.86 – 1.99) | 0.20 |
| Hyperlipidaemia | | 0.89 (0.55 – 1.45) | 0.64 |
| IHD | | 1.06 (0.60 – 1.88) | 0.85 |
| Liver disease | | 2.56 (0.60 – 10.87) | 0.20 |
| **Medicine related** | | | |
| No. admission medicines | | 1.04 (1.00 – 1.09) | 0.07 |
| No. discharge medicines | | 1.10 (1.05 – 1.16) | <0.0001 |
| Previous ADR | | 1.22 (0.80 – 2.00) | 0.31 |
| MCA | | 0.98 (0.66 – 1.48) | 0.94 |
| Antithrombotic at discharge | | 1.71 (1.12 – 2.60) | 0.01 |
| Antidiabetic at discharge | | 1.28 (0.78 – 2.08) | 0.33 |
| Antihypertensive at discharge | | 1.55 (1.03 – 2.33) | 0.04 |
| **Frailty measures** | | | |
| Hand Grip | | | |
| Female (kg) | | 1.02 (0.98 – 1.07) | 0.31 |
| Male (kg) | | 0.93 (0.89 – 0.98) | 0.008 |
| Falls | 0 | 1.00 | |
| | 1 | 0.70 (0.40 – 1.22) | 0.20 |
| | >1 | 0.76 (0.48 – 1.21) | 0.25 |
| **Dependency in ADLs** | | | |
| Barthel Index | | 0.98 (0.94 – 1.03) | 0.44 |

Table 5.4 cont. Univariate analysis of potential predictor variables for MRH (based on binary logistic regression)

| Variables | Odds ratio (95% CI) | p |
|---|---|---|
| **Social circumstances** | | |
| Care frequency | | |
| 0 | 1.00 | |
| 1 – 3 times per day | 1.50 (0.90 – 2.48) | 0.13 |
| 4 – 6 times per day | 1.58 (0.96 – 2.62) | 0.08 |
| 24 hr care in institution | 0.65 (0.27 – 1.55) | 0.33 |
| Lives alone | 1.28 (0.83 – 1.97) | 0.29 |

ADLs: activities of daily living; ADR: adverse drug reaction; AMTS: abbreviated mental test score; CCF: congestive cardiac failure; CCI: Charlson comorbidity index; eGFR: estimated glomerular filtration rate; IHD: ischaemic heart disease; MCA: multi-compartment compliance aid; MUST: malnutrition universal screening tool

Being prescribed antithrombotics (which included antiplatelets and anticoagulants) at discharge was significantly associated with MRH. It is unclear if this association was due to the high-risk nature of these medicines and their propensity to cause distressing side effects such as bruising or bleeding, or the clinical indication for which they were prescribed. More patients with MRH had atrial fibrillation (31%) than those in the no MRH group (23%), but this difference was not statistically significant (p = 0.08). Based on the recommendations of NICE[227] (which advocates the use of $CHA_2DS_2$-VASc score[228] to estimate stroke risk in patients with non-valvular AF), it is likely, due to their age alone being a substantial risk factor (most were ≥75 years old), that the majority of the study population with AF were receiving antithrombotic treatment. Multi-collinearity between these variables is therefore probable, however this was not tested for.

Care frequency was not significantly associated with MRH however the result tended towards greater support needs at home, as suggested by the need for a four times a day or more care package, being associated with the risk of MRH. Interestingly, this relationship was not seen with the highest level of support defined as 24-hour care in an institution.

### 5.4.2 Re-admissions

Over one third (n=156 (39.4%)) of patients were re-admitted during the 8-week follow up. The baseline demographics for re-admitted patients and the whole study population is provided in Table 5.5. Age, gender and ethnicity were similar but overall re-admitted patients were more frail. Re-admitted patients had a higher CCI (2.3 (SD 1.6) compared to 2.1 (SD 1.6)), were prescribed on average 1 more discharge medicine, and were more likely to use an MCA to assist in the management of their medicines. They had a higher level of dependency in ADLs (mean Barthel Index 12.6 (SD 4.3) compared to 13.2 (SD4.6)) and greater levels of sarcopenia in both sexes but especially in men (mean hand grip: female 11.9 (SD 5.9) kg, male 18.3 (SD 6.9) kg compared to female 12.2 (SD 5.8) kg, male 19.9 (7.3) kg). Over two thirds (68%) of the patients who died during the 8-week follow up were re-admitted.

Table 5.5 Baseline demographics of re-admitted patients and not re-admitted patients

| **Characteristic** | **Number of patients (%)** | | |
|---|---|---|---|
| | **Re-admitted (n=156)** | **Not re-admitted (n=240)** | **All study patients (n=396)** |
| **Demographics** | | | |
| Gender (female) | 99 (63) | 157 (65) | 256 (65) |
| Age (years)^ | 83 (7.2) | 84 (6.9) | 83 (7.0) |
| Ethnicity (white) | 140 (90) | 213 (89) | 352 (89) |
| **Clinical** | | | |
| CCI^ | 2.3 (1.6) | 2.1 (1.7) | 2.1 (1.6) |
| AMTS^ (range 0-10) | 8.3 (1.7) | 8.3 (1.8) | 8.3 (1.7) |
| MUST† | | | |
| 0 | 82 (55) | 127 (53) | 209 (55) |
| 1 | 29 (19) | 43 (18) | 72 (19) |
| 2 | 38 (26) | 61 (25) | 99 (26) |
| **Medicine related** | | | |
| No. discharge medicines^ | 11.1 (4.4) | 9.4 (4.2) | 10.1 (4.4) |
| MCA† | 80 (51.3) | 92 (38.8) | 172 (45.9) |
| **Frailty measures** | | | |
| Hand Grip^ | | | |
| Female (kg) | 11.9 (5.9) | 12.3 (5.8) | 12.2 (5.8) |
| Male (kg) | 18.3 (6.9) | 21.0 (7.3) | 19.9 (7.3) |
| Falls (>1 in 12months)† | 80 (51.3) | 105 (43.8) | 185 (46.8) |
| **Dependency in ADLs** | | | |
| Barthel Index^ (range 0-20) | 12.6 (4.3) | 13.6 (4.7) | 13.2 (4.6) |

^ Mean (SD); †missing data: MUST n=380, MCA n=395, falls n=395

AMTS: abbreviated mental test score; CCI: Charlson comorbidity index; MCA: multi-compartment compliance aid; MUST: malnutrition universal screening tool

The distribution of time to re-admission of the study population is presented in Figure 5.1. Almost half (49%) of re-admissions occurred within the first 14 days, which is similar to that of the OPU population in general.

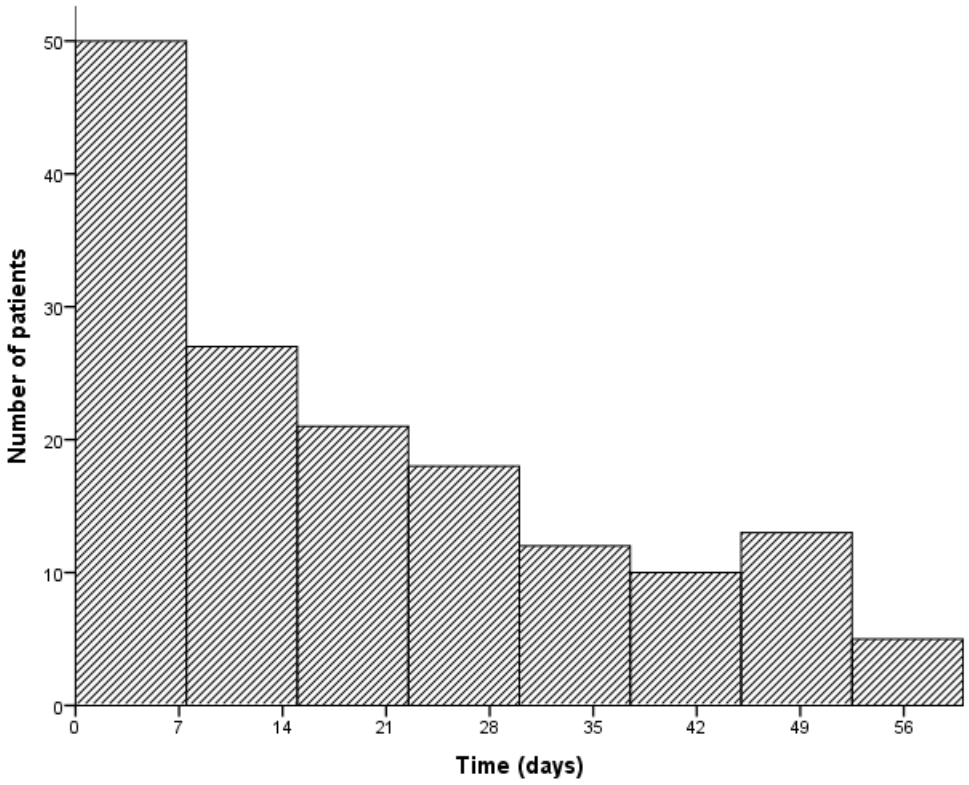



Figure 5.1 Distribution of re-admission of the study population (n=156)

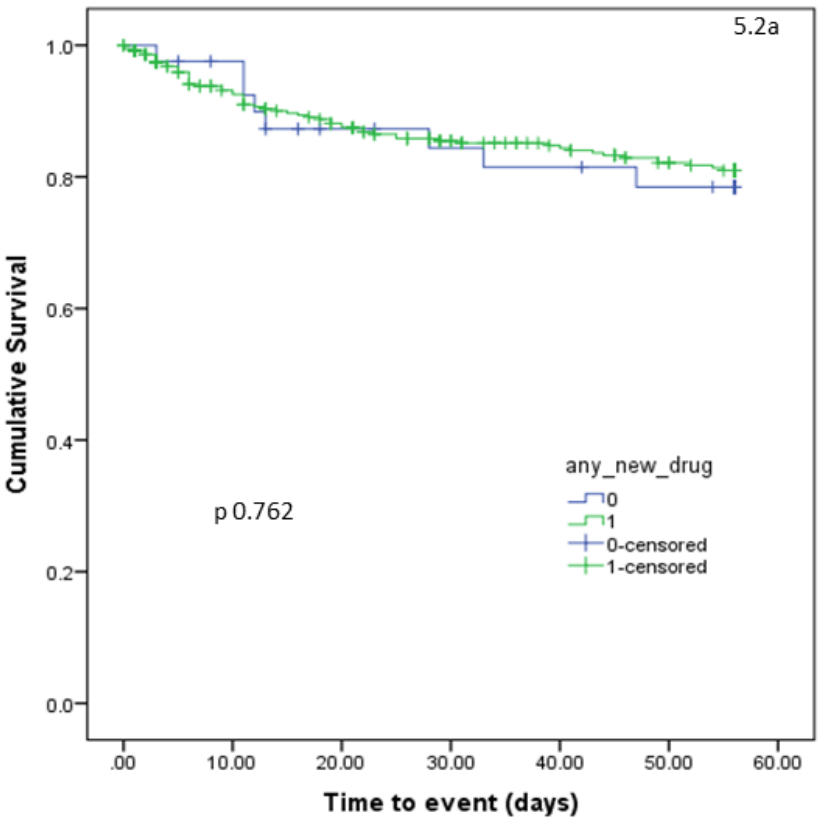
#### 5.4.2.1 Comparison of patients with MRH re-admission to those without

Of the 396 patients included in the study, 67 were readmitted with MRH. Survival analysis revealed a mean time to event of 48.9 days (SE 0.84; 95% CI 47.3-50.6). Table 5.6 summarises the relationship between the independent variables and MRH re-admission. Significant associations were found with variables across a range of categories. Using an MCA, number of medicines, CCI and depression were all found to be statistically significant following survival analysis. The significance of falls and care frequency was borderline. Kaplan-Meier curves are presented in Figure 5.2 - Figure 5.5.

Table 5.6 Analysis of variables for MRH re-admission (based on survival analysis)

| **Variable** | **Statistical association** | |
|---|---|---|
| **Kaplan-Meier** | **chi square** | **p** |
| New medicine | 0.091 | 0.762 |
| MCA | 9.762 | 0.002 |
| Falls 0-1,>1 | 3.571 | 0.059 |
| AMTS<8 | 0.348 | 0.555 |
| Care package | 5.934 | 0.051 |
| Previous ADR | 0.889 | 0.346 |
| Ethnicity | 0.697 | 0.404 |
| Gender | 0.330 | 0.566 |
| **Cox regression** | **Hazard Ratio (HR) (95% CI)** | **p** |
| Number of drugs | 1.101 (1.05-1.154) | <0.01 |
| MUST | 1.083 (0.821-1.426) | 0.573 |
| Barthel | 0.973 (0.925-1.024) | 0.299 |
| CCI | 1.142 (1.012-1.29) | 0.032 |
| Mobility | 0.916 (0.752-1.115) | 0.381 |
| Age | 0.995 (0.962-1.03) | 0.779 |
| Length of stay | 0.995 (0.976-1.014) | 0.589 |
| Depression | 1.044 (1.007-1.082) | 0.019 |
| Anxiety | 0.970 (0.861-1.093) | 0.614 |

ADR: adverse drug reaction; AMTS: abbreviated mental test score; CCI: Charlson comorbidity index; MCA: multi-compartment compliance aid



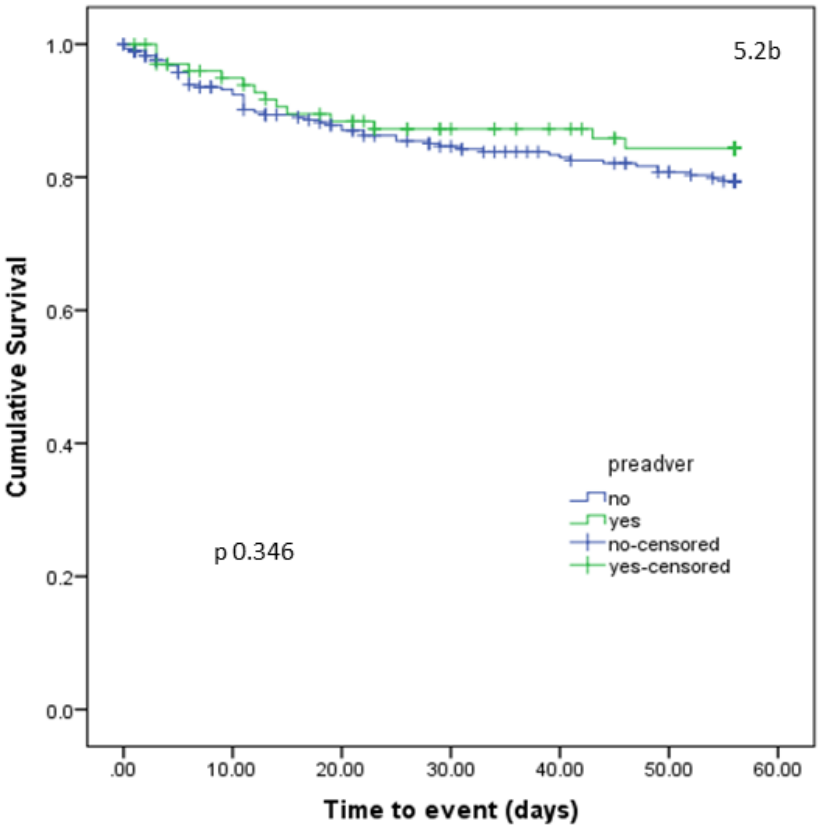
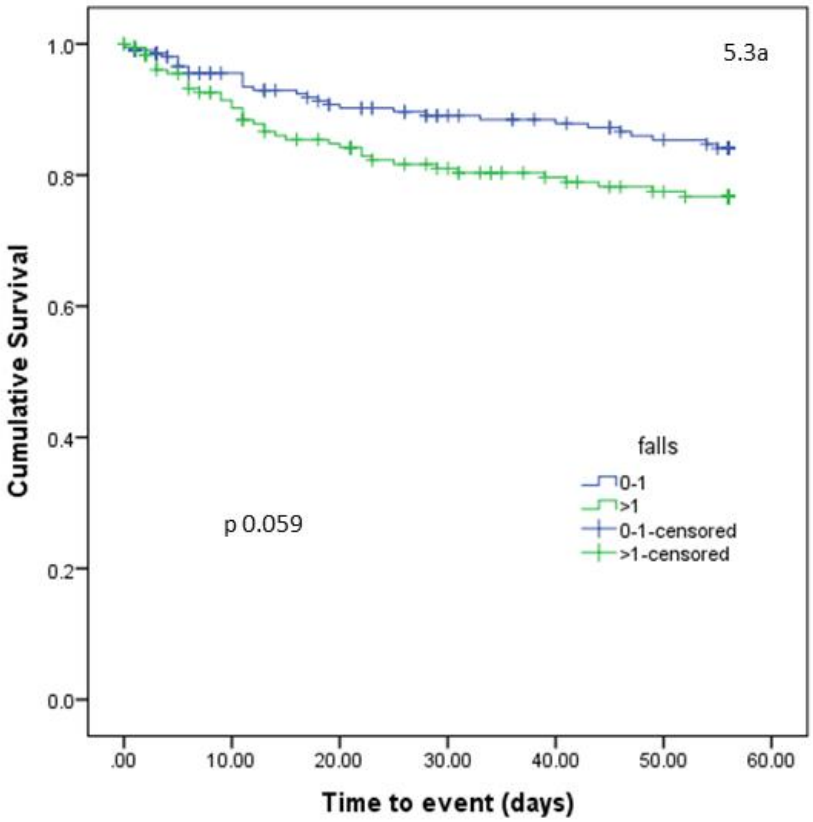




Figure 5.2 Kaplan-Meier curves showing relationship between MRH re-admission and any new drug (5.2a), and previous ADR (5.2b)



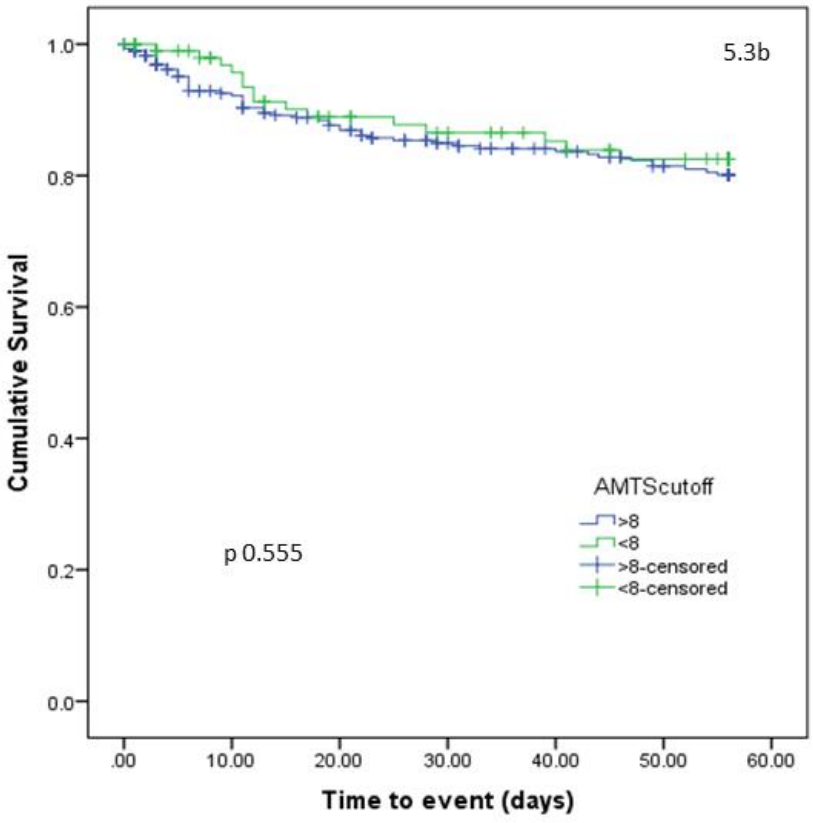
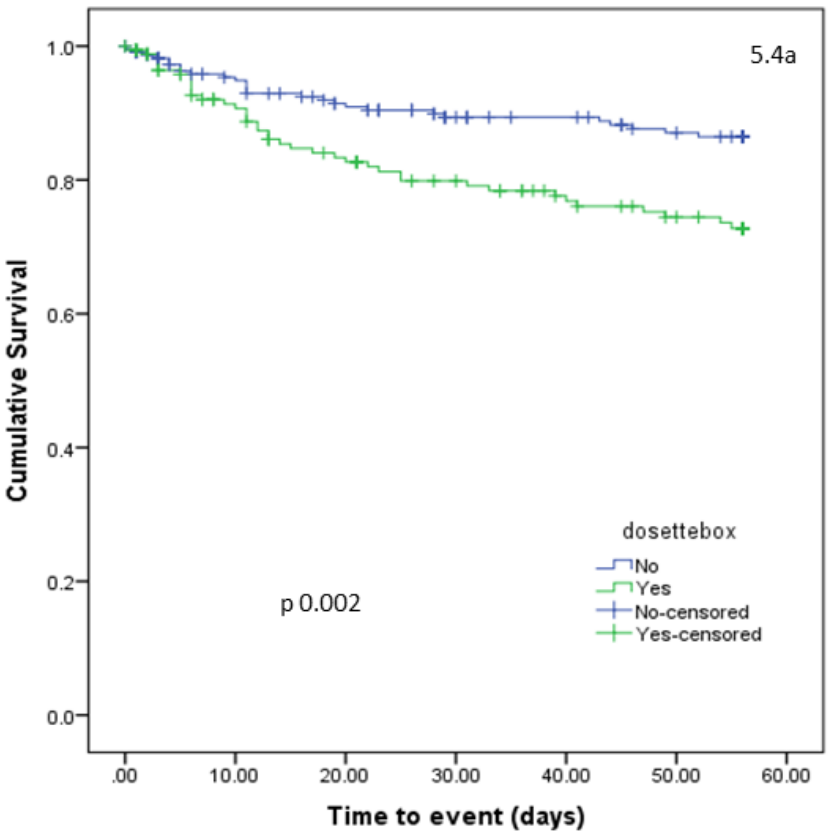




Figure 5.3 Kaplan-Meier curves showing relationship between MRH re-admission and falls (0-1 or >1 in 12 months; 5.3a), and AMTS score (5.3b)



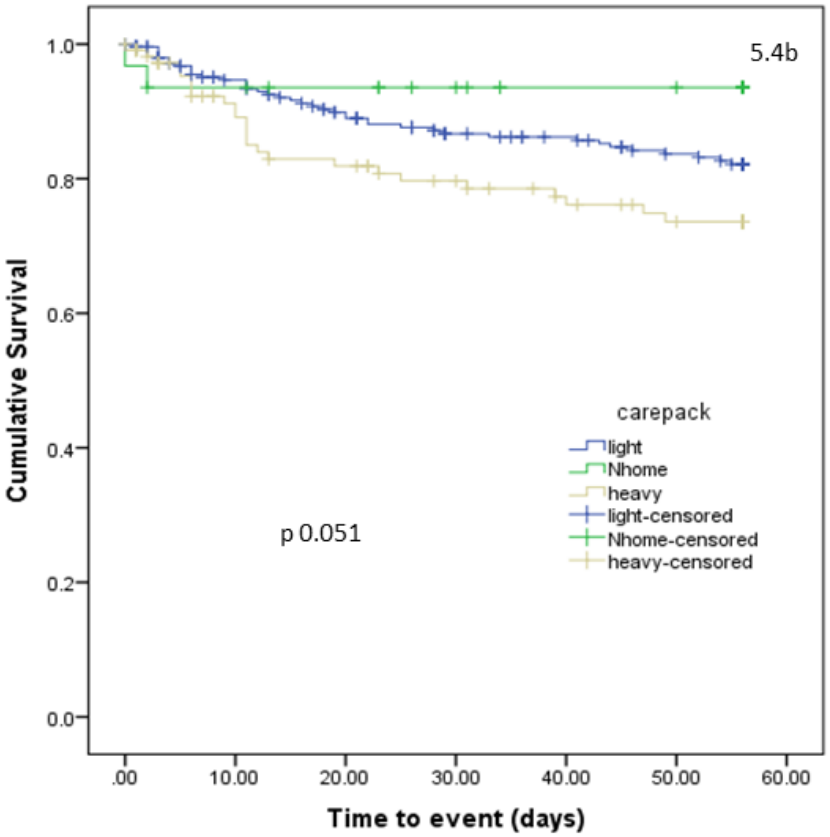
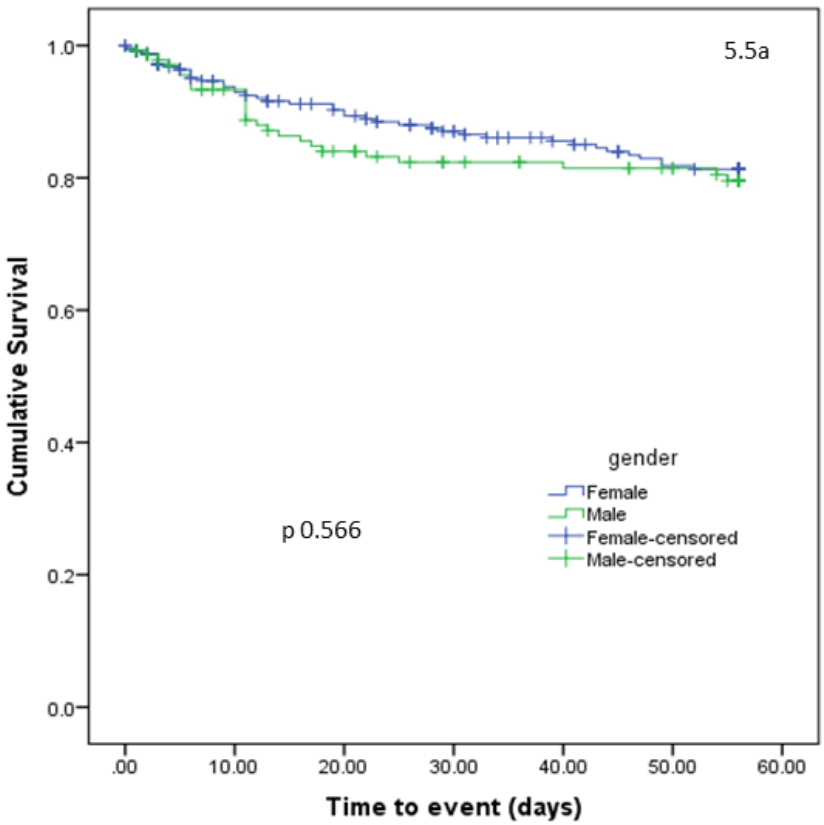




Figure 5.4 Kaplan-Meier curves showing relationship between MRH re-admission and use of an MCA (dosette box) (5.4a) and intensity of home support (light = 0-3 times/day, heavy = >4 times/day and institutional care); (5.4b)



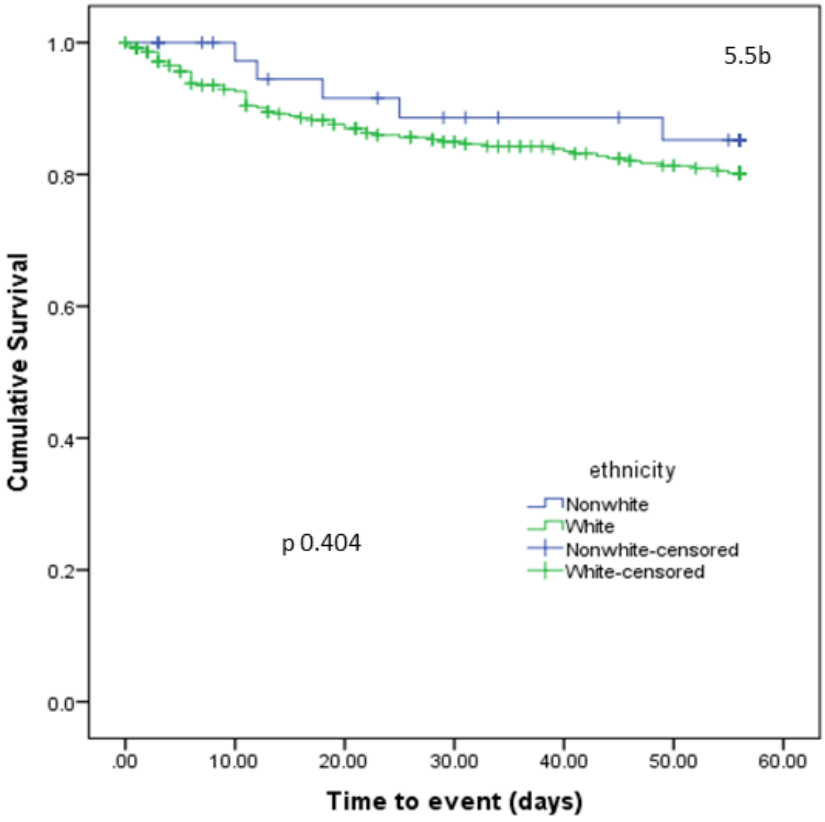




Figure 5.5 Kaplan-Meier curves showing relationship between MRH re-admission and gender (5.5a), and ethnicity (white or non-white; 5.5b)

Multicollinearity is expected to exist between these variables and so must be tested for, e.g. the more comorbidities diagnosed (as represented by CCI) the more medicines prescribed. To test for multicollinearity, statistically significant variables, and those approaching significance, were included in a multivariate model (see Table 5.7). The number of medicines was the only variable that retained significance. Falls and depression, whilst tending towards an association with MRH, were not statistically significant, and adjusting for age and gender made minimal difference to the model.

Table 5.7 Multivariate Cox regression model of independent variables (adjusted for age and gender)

| **Factor** | **HR** | **Lower CI** | **Upper CI** | **p** |
|---|---|---|---|---|
| Number of medicines | 1.08 | 1.025 | 1.138 | 0.004 |
| MCA | 1.535 | 0.908 | 2.593 | 0.11 |
| CCI | 1.074 | 0.932 | 1.239 | 0.323 |
| Falls | 1.556 | 0.936 | 2.587 | 0.088 |
| POC light | | | | 0.226 |
| POC NH | 0.377 | 0.089 | 1.586 | 0.183 |
| POC heavy | 1.267 | 0.748 | 2.145 | 0.378 |
| Depression | 1.039 | 0.996 | 1.083 | 0.077 |

CCI: Charlson comorbidity index; CI: confidence interval; HR: hazard ratio; NH: institutional care; MCA: multi-compartment compliance aid; POC: package of care

#### 5.4.2.2 Comparison of patients re-admitted with and without MRH

To further explore the relationship between MRH and frailty, a comparison of MRH re-admission (n=67) and non-MRH re-admission (n=89) and the associations with frailty indicators was conducted. As shown in Figure 5.6, at univariate analysis, CCI and the number of medicines were associated with an increased risk of MRH re-admission, ($p<0.05$), OR 1.227 (95% CI 0.998-1.508, p0.053) and OR 1.082 (95% CI 1.005-1.166, p0.037), respectively. As previously mentioned, these are likely to be correlated but this was not tested. As only 2 patients from institutional care were re-admitted, and neither instance was due to MRH, this group could not be included in the analysis. All other frailty indicators did not demonstrate a significant association with MRH re-admission.

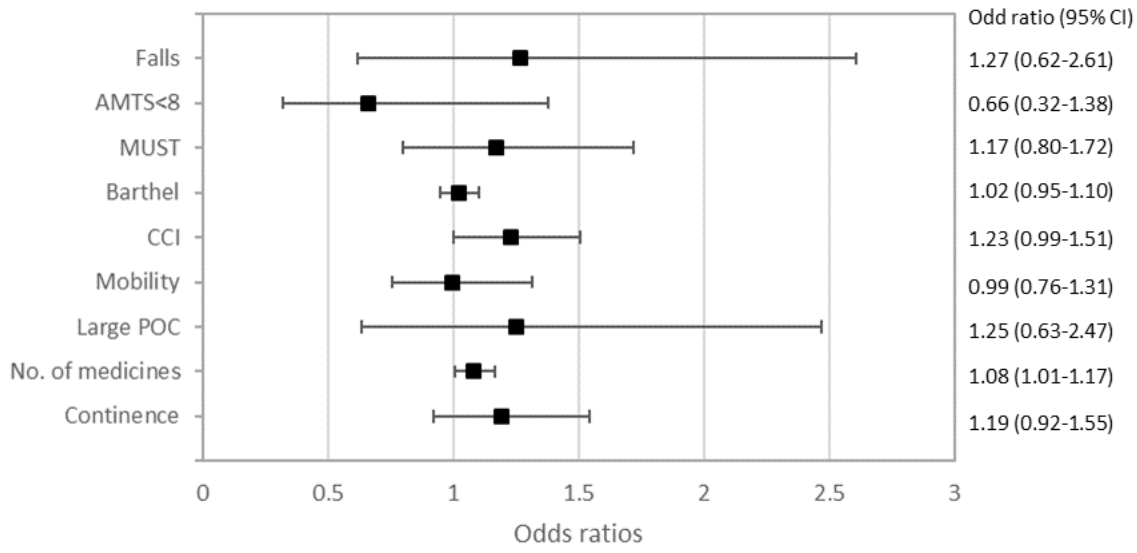



Figure 5.6 Comparison of MRH re-admission and non-MRH re-admission

### 5.4.3 Severity of MRH and healthcare utilisation

In this study, a severity rating of "serious" was defined as 'an additional visit to clinic for treatment or additional medications, including dose reductions or cessation of therapy'.[22] Due to the scope of this definition all re-admissions were classed as at least serious MRH, however not all serious MRH had to result in re-admission. The same serious MRH may also be managed through self-care at home or a GP consultation. The concept that different types of healthcare utilisation may be sought by different individuals, in response to the same severity of MRH, was introduced in Chapter 3 (Figure 3.5). This action is likely to be influenced by both their physiological and psychosocial reserve. Figure 5.7 describes three cases of serious MRH where the patient developed constipation as a result of an ADR, or a combination of ADR and non-adherence. The consequential healthcare utilisation is also outlined.

**Case 1: Serious – self-management**

MRH event: constipation (ADR and non-adherence)

92 year old female. Lives with daughter, no formal care package. Past history of OA, CKD, colorectal Ca, hyperlipidaemia, hypertension. Previous allergies/ADR: Rash from ACE inhibitors. Discharged from hospital following pubic rami fracture. Co-codamol 30/500mg QDS initiated as inpatient and continued on discharge. Macrogol 1 BD and senna 15mg ON PRN also prescribed but patient was non-adherent. Developed constipation so commenced laxatives and normal bowel movements were resolved.

**Case 2: Serious – GP managed**

MRH event: constipation (ADR)

79 year old female. Lives alone, no care package. Past history of COPD, AF, hypertension, IHD (previous MI), depression. Previous allergies/ADR: cough with ramipril. Co-codamol 8/500mg 2 QDS initiated to treat back pain. After 7 days contacted GP because she was constipated. GP diagnosed constipation and advised to stop co-codamol. Regular paracetamol, tramadol PRN were commenced for pain and senna and lactulose for constipation.

**Case 3: Serious – hospital admission**

MRH event: constipation (ADR and non-adherence)

86 year old female. Lives alone in "extra care" sheltered accommodation with QDS carers. Past history of type 2 diabetes, hypertension, hyperlipidaemia, diastolic dysfunction, peripheral vascular disease, neuropathic pain, previous stroke (residual left hemiplegia), wheelchair bound, cataracts. Previous allergies/ADR: Unknown nature of intolerance to beta-blockers, ramipril, co-proxamol and glibenclamide; rash with penicillins. During index admission buprenorphine patch initiated in hospital for shoulder pain, and regular lactulose for constipation. Patient was prescribed Senna PRN prior to admission and this was continued. Buprenorphine dose increased in community due to uncontrolled pain. Two weeks later presented to A&E with abdominal pain and was diagnosed with acute on chronic constipation. Advised to take regular laxatives – macrgol commenced. Re-presented four days later with ongoing lower abdominal pain, not eating or drinking and no bowel motions. Due to reduced oral intake carers were concerned about continuing insulin and so sent patient to A&E. Compliance with laxatives unclear – lactulose and senna issued by hospital (outside of MCA) following index admission but was not on GP records so further supply unlikely. Re-admitted with constipation.

ACE: angiotensin converting enzyme; ADR: adverse drug reaction; AF: atrial fibrillation; BD: twice per day; Ca: cancer; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; IHD: ischaemic heart disease; MCA: multi-compartment compliance aid; MI: myocardial infarction; MRH: medication related harm; OA: osteoarthritis; ON: at night; PRN: when required; QDS: four times per day.

Figure 5.7 Case studies describing serious MRH (constipation) and the resultant healthcare utilisation

Considering the cases outlined in Figure 5.7, it may be argued that the overall resilience (both physiological and psychosocial) declines as the level of healthcare utilisation increases. Case 1, whilst being the oldest patient, had a relatively simple past medical history and living with her daughter provided a robust psychosocial system and as a result, she was able to self-manage the constipation. By comparison, Cases 2 and 3 had more complex medical histories and were likely to have less physiological reserve. In Case 2, social isolation and a history of depression were likely to limit the psychosocial resilience. In combination, the limitations within both physiological and psychosocial systems lead to the patient requiring GP support to manage her constipation. Finally, in Case 3 the patient suffered from multimorbidity and was heavily dependent upon formal care to support her ADLs and so had extensive levels of impairment in both physiological and psychosocial systems. She was ultimately sent to hospital by her carers for the management of her constipation.

## 5.5 Discussion

This is the first study to explore previously validated variables alongside those where little prior research has been undertaken. The analysis found associations between MRH and a range of variables from both physiological and psychosocial clusters but, apart from the number of medicines prescribed at discharge, none retained significance when included in a multivariate model. This research programme has highlighted the heterogeneity of this population who present to the health services with not only a diverse range and combination of clinical conditions, but with extensive variability in their functional ability, and psychological and social support mechanism, which is likely to make the identification of a discrete number of highly predictive variables challenging.

When comparing the findings of this research to previous findings a number of issues are worth considering. Firstly, patients are generally older and receive more prescribed medicines. This is partly driven by increased life expectancy coupled with multimorbidity[48] and the ensuing guideline-based prescribing[218,219], as evident from the number of medicines prescribed in earlier studies in the systematic review being less than this study cohort. Secondly, despite the lack of significance at multivariate level, some interesting findings were noted which suggest that as well as the more traditional variables, such as number of medicines and specific medicines classes, the

psychosocial variables are likely to influence the occurrence of MRH. These findings include use of a multi-compartment compliance aid, depression, malnutrition, low hand grip (men only) and having a large package of care at home being associated with post-discharge MRH. The lack of demonstrated independent association can in part be explained by the relatively small sample studied, as well as the possible complexity of the relationship between variables. Furthermore, whilst the variables explored in the psychosocial cluster explored some of the aspects of frailty it was by no means complete. As our understanding of the variables that influence frailty progresses this will direct future work to ensure that the variables included represent a better understanding of the frailty domains.

This study has confirmed the association between a range of variables and MRH at a univariate level. The number of medicines demonstrated a significant association with MRH in all analyses, a finding consistent with the wider literature. This is unremarkable given that it would be anticipated that patients are more likely to experience MRH when they are prescribed more medicines. Given the high prevalence of overall low reserve in the patient group, the number of medicines may represent both a greater clinical illness burden, and an increasing likelihood of exposure to a potential medication related insult, and consequentially an increased likelihood of experiencing MRH. Interestingly, the effect size for the number of medicines reported across the literature varies, and is influenced by whether this variable is analysed as a continuous or dichotomised variable. The odds ratios (95% CI) for the number of medicines variable were: 1.10 (1.05-1.16) compared to 3.30 (1.93-5.65) Tangiisuran[85], 4.07 (2.93-5.65) Onder[18], 1.9 (1.6-2.3) Trivalle[88]. This variance may be due to the different primary outcome measures studied or the use of non-standard definitions which, as discussed in Chapter 3, is a challenge when interpreting research in this area. However, it should also be noted, that both Tangiisuran[85] and Onder[18] categorised the number of medicines based on an "optimal" cut-off point of ≥8 medicines. Altman and Royston[127,229] advise against adopting this technique of arbitrary dichotomisation due to the increased likelihood of a Type 1 error occurring thereby over-estimating the difference between the two groups. Indeed, dichotomisation of the number of medicines variable using the cut-off point of ≥8 medicines in this study results in an odds ratio of 2.45 (95% CI 1.52-3.92, $p<0.0001$), more than doubling the effect size. In the systematic review studies, many continuous variables were dichotomised or split into multiple categories e.g. number of comorbidities, renal function, age, antihypertensives, and so further comparison is of limited value.

Antithrombotics were significantly associated with MRH at a univariate level which is consistent with previous studies[85,88] and is unsurprising given the high-risk nature of these medicines. Associated with serious and potentially distressing side effects, such as bruising and bleeding, patients are counselled on the importance of identifying and reporting these side effects, as they may be a sign of over treatment. As a result, patients may be better educated about the risk profile of these drugs, increasing reporting and documentation of these ADRs in their medical notes. A true increased risk of harm from medicines within this class however is likely, as demonstrated by a recent large prospective cohort study[230]. It found that those over the age of 75 years old admitted to hospital with their first transient ischaemic attack, ischaemic stroke or myocardial infarction and treated with antiplatelet therapy (mainly aspirin), without routine proton-pump inhibitor (PPI) use had a significantly higher risk of major bleeding events than younger patients (HR 3·10, 95% CI 2·27-4·24; p<0·0001). This risk was even higher for major upper gastrointestinal bleeds (HR 4·13, 2·60-6·57; p<0·0001), particularly if disabling or fatal (10·26, 4·37-24·13; p<0·0001).[230]

Being prescribed an antihypertensive has previously been identified as a risk factor for MRH and was confirmed in this current study. A combination of antihypertensives, with different mechanisms of action, were frequently prescribed in the study population. This is unremarkable given the prevalence of hypertension in this population, and in line with national guidance. The use of multiple antihypertensives with similar therapeutic and adverse outcomes could overwhelm an already compromised system in a frail older population. For example, an 86 year old female study participant was re-admitted to hospital following a two day history of urinary frequency, burning upon micturition, fevers and dizziness. Amongst her comorbidities were severe aortic stenosis and ischaemic heart disease and, her prescription medicines included; losartan, diltiazem, nicorandil and isosorbide mononitrate. Urinalysis tested positive for a urinary tract infection (UTI). Upon admission her blood pressure was slightly elevated (155/72mmHg), however following administration of her medicines it dropped to 95/40mmHg and she described the same dizzy feeling as prior to admission. She was diagnosed with a hypotensive episode secondary to antihypertensives on a background of a UTI and severe aortic stenosis. Nair and colleagues[68] also reported that the more antihypertensives prescribed the higher the risk of hospitalisation due to ADR but with a greater effect size OR 4.75 [95% CI 1.89-11.93, p0.001]

compared to the current study OR 1.55 [95% CI 1.03-2.33, p0.04]), most likely due to categorisation of the continuous variable.

Comorbidity was significantly associated with MRH at a univariate analysis level but significance was not maintained in a multivariate model. This is consistent with the findings of Nair[68] and Trivalle[88], however Onder[18] reported significance at multivariate level and Tangiisuran[85] found no association. Some of the variation may be explained by: the different method of measurement used, for example this current study used the Charlson comorbidity index in comparison to the systematic review studies which used disease count; or the type of analysis used, different cut-off points were used to dichotomise the number of comorbidities variable. Unlike previous MRH risk prediction studies[18,68], depression was found to be significant at a univariate level in this study, HR 1.04 (95% CI 1.01-1.08, p0.019). The relationship between depression and MRH has been reported in the wider literature and is consistent with the findings of this study; Onder and colleagues[231] in a study of 3134 older inpatients (mean age 72.0±14.1 years) found depressed patients (classified using the Geriatric Depression Score) had a higher risk of ADR than patients without depression, adjusted OR 1.58 (95% CI 1.14-2.20). With regards to non-adherence, in a meta-analysis of the effects of depression on patient adherence, which identified 13 studies, those with depression were found to be three times more likely to be non-adherent to medical treatment[232] and as demonstrated by this current study, non-adherence was responsible for approximately a third of all MRH. The associations of liver disease and hyperlipidaemia with the risk of MRH remain unclear with the current study, along with some of the systematic review studies[68,85], not reporting a significant relationship whilst others[18,85] did, even at multivariate level.

A unique aspect of this study was the exploration of variables which have either not previously been researched or only in a limited fashion, with regards to predicting MRH. The use of a MCA was significantly associated with MRH re-admission at a univariate level, which is perhaps surprising as they are a commonly used intervention aimed at supporting medicines use, however recent research questions their value. The REMIND study[233] was a comparative-effectiveness randomised controlled trial of three adherence support devices, including a MCA, involving over 50,000 patients in the United States. Almost 18,000 patients prescribed between one and three medicines for cardiovascular disease, diabetes, non-depression related chronic disease or depression were randomised to receive a MCA and followed up for 12 months. The authors found that adherence was not improved by any of the devices. In addition, a study of 2060 adult MCA

users in Scotland, with a median age of 82 (IQR 70-87) years, found patients using a MCA had an increased likelihood of being prescribed a potentially inappropriate medicine[234] and so could have an increased risk of experiencing MRH.

The association of MRH and care package was significant at a univariate level and was more significant in individuals who had a large care package at home than for those individuals requiring round the clock care, for example in a nursing home. Although individuals requiring institutional care are likely to have greater physiological deficits than those managed at home, it would seem that the resources available to them to withstand setbacks within institutional care reduces the risk of experiencing a re-admission with MRH.

A MUST score of 1 was significantly associated with post-discharge MRH. An interdependent relationship between ADRs and nutritional status has been described where ADRs, such as nausea or taste disturbances, may influence nutritional intake which may then impact on the risk of ADRs through altered drug pharmacokinetics[235] e.g. compromised nutritional status can result in reduced hepatic protein synthesis, in particular albumin, thereby reducing the protein-binding capacity of the drug and increasing the concentration of free drug which increases the risk of toxicity.

Hand grip has not been explored previously in the context of MRH and a low hand grip (males only) was found to be significantly associated with post-discharge MRH univariate level. A measure frequently considered when assessing frailty, this association may be highlighting that frail individuals are at greater risk of MRH due to decreased homeostatic reserve and so they have limited reserve to cope with minor insult.

Whilst many of the variables whose relationship with MRH had not previously been explored were significantly associated with MRH upon univariate analysis (MCA use, care package, MUST score and hand grip), none retained significance in a multivariate model which is likely due to multicollinearity.

The inconsistencies across the studies between variables identified as being associated with MRH may be explained by the different study populations, the different clinical context (that is, post-acute illness in this study) and the considerable heterogeneity that exists in older populations. The limited reporting of baseline characteristics restricts the ability to compare this

study population and the populations investigated in the development of the existing risk prediction models[18,68,85,88,89], however where data were available it suggests that the current study population was more frail. Only Onder[18] reported CCI and it was lower than in this study population (1.46 (SD 1.75) versus 2.1 (SD 1.6) respectively). Although the demographics of this study population were similar to the populations investigated by Tangiisuran[85] and Trivalle[88] (the majority of patients were over the age of 80 years old, white and female), this study population were more dependent in their activities of daily living with a mean Barthel Index score of 13 (SD 4.6) compared to Tangiisuran[85] who reported 19 (range 14-20). More of this study population lived alone (62.5%) when compared to the population investigated by Tangiisuran (57%)[85].

Co-morbidities represented a spectrum of conditions in all studies, suggestive of multimorbidity in all the populations. The older studies reported the lowest number of prescribed medicines, with Onder[18] reporting the least, followed by Tangiisuran[85] and Trivalle[88]. More recent studies, including this study and the study by Nair[68], both report a mean of over 10 medicines per patient.

Overall, where comparison of study populations was possible, the current study population appears to have more deficits across multiple domains than the systematic review study populations and so has a greater risk of MRH as reflected by the higher MRH incidence in this study and re-admission rate.

The re-admission rate seen in this study, was found to be more than three times higher than that of the Older Persons Unit population in general; during the 28 days after discharge 28.3% of the study cohort was re-admitted compared to 8.4% of the OPU population. The OPU figures represent a slightly different time period, during which a new admission avoidance service was introduced. This may have resulted in the more stable patients being treated at home: this would likely result in the mean readmission risk being higher in those who were admitted. In addition, the new service may have directly reduced the number of OPU re-admissions, but it is unlikely that these possibilities fully explain the magnitude of observed difference in readmission rate. It is more likely that the study population is not representative of the OPU population.

### 5.5.1 Limitations

As previously discussed in Chapter 4, the complexity of this population makes determining the cause of MRH challenging. Only a quarter (24%) of cases were classed as definitely due to MRH. This can result in some event misclassification and so the potential impact on the statistical associations between variables and MRH needs to be considered.

Recruitment to the study was challenging, partly due to difficulties in consenting a frail older population, and so a small sample size limited some of the analysis. For example, only 67 patients experienced MRH re-admission which should be recognised when interpreting the results as this presents an increased risk of Type II error during statistical analysis. As a result, firm conclusions could not always be drawn from the data but the trends identified support the hypothesis of this exploratory study and warrant further investigation.

To fully utilise the data available, dichotomisation, or categorisation of continuous variables, was avoided where possible. Whilst this is a long-standing practice in risk prediction research, often justified by researchers as improving the clinical utility of risk prediction models, it is heavily criticised by statistical experts as it can result in over-optimism of effect size. In the current study, AMTS score and number of falls were dichotomised, however AMTS was also analysed as a continuous variable with no noteworthy change in association. It would be beneficial to analyse falls as a continuous variable; however the cut-off point utilised was reflective of that used in clinical practice in distinguishing between a one-time faller and a frequent faller, the latter being associated with frailty.

Another challenge of research in this area is the vague reporting of episodes of MRH by patients and in medical notes, which make it difficult to determine the exact date that MRH commenced or was experienced. Since a key component of survival analysis is an accurate event date, survival analysis could only be applied to re-admission data.

The high re-admission rate of the study population in comparison to the general OPU may be suggestive of recruitment bias, whereby those who were less unwell were discharged quicker and therefore missed during recruitment. The resultant study population was therefore more unwell, and more at risk of re-admission, thus limiting the generalisability of the findings. This should not detract from the high re-admission rate and high overall incidence of MRH, which is important

with regards to service improvement, especially as this population reflects the advancing complexity of geriatric medicine.

## 5.6 Conclusion

This exploratory work has identified the complexity of the associations between variables and MRH, and the potential impact of psychosocial variables on MRH. Psychosocial and frailty related variables, were associated with MRH risk, although statistical significance of each individual variable was not demonstrated in the multivariate model. The heterogeneity of the population, due to advancing age[236] and frailty, makes the identification of a small number of highly predictive variables challenging, and may limit the usefulness of pursuing the path of identifying a set of strongly predictive variables. Furthermore, not only are an individual's risk factors wide-ranging, they are also dynamic, improving or worsening at any given time point. The clinical context of this study was one during which the patients conditions were likely unstable for most, with some recovering, some relapsing, and some having new conditions. As described in the conceptual framework, when physiological and/or psychosocial reserves are limited, e.g. when the multiple deficits are combined, then the likelihood of harm increases. In the context of MRH, multiple deficits increase the likelihood of a patient experiencing MRH, and the more medicines a patient is prescribed, the greater the chance of harm occurring. With an aging population, it's imperative that we better understand the complexity of MRH if we hope to reduce burden on the patient and the NHS.

# Chapter 6 Discussion

## 6.1 Principal findings

This research set out to examine the possibility of identifying older patients at risk of MRH following an acute hospital episode. The studies which form this thesis assessed the occurrence of MRH during the post-discharge period, and also focused on the identification of existing MRH risk prediction models and the exploration of variables associated with MRH.

The systematic review identified five MRH risk prediction models for use in older adults, all focussing on ADRs, none of which were designed to assess the risk after an acute hospital episode. A number of issues were identified relating to the quality of the existing studies and the accuracy of the models developed, preventing their adoption into routine practice. Moreover, the models failed to address the complexity of the older population, and the breadth of variables required to capture such variation. Work to date has focussed on more traditional variables relating to disease, its management and the associated risks e.g. number of co-morbidities, number of medicines and level of dependency for ADLs. There is a lack of understanding of the role of psychosocial support received by older patients in mitigating the risk of harm from medicines.

The prospective cohort study found that almost 40% of frail older patients discharged from hospital following an acute admission experienced at least one episode of MRH, the majority of which (88%) required treatment modification and were considered preventable (58%). A significant level of healthcare utilisation relating to MRH was identified with 1.2 episodes of care per MRH event, most of which involved consultation with a GP (59%). Re-admissions were common with two in five patients re-admitted within 8 weeks of discharge, 43% of which were due to MRH and three quarters were considered preventable.

Further analysis confirmed the importance of the number of medicines and the risks associated with particular classes of medicines, e.g. antithrombotic agents, when identifying patients at high-risk of MRH, but has also uncovered factors associated with risk which were previously thought to be supportive, e.g. the use of a MCA. Hand grip (men only), a MUST score of 1, depression and comorbidity were also associated with MRH, however the only variable to demonstrate an independent association following multivariate analysis was the number of medicines at discharge.

The generalisability of the results from this research may be limited given the unique patient cohort who, due to recruitment from the specialist older persons unit only, represent a frail older population. Whilst recognising this limitation it should be considered that the population studied is likely to reflect the future older patient discharged from hospital as healthcare services focus upon reducing the unnecessary admissions of older adults, and increasing care in the community, so limiting hospital admission to the most complex and frail. A further limitation is the potential for event misclassification due to the difficulty of determining causality in such a complex population; this may have impacted on the strength of associations between certain variables and MRH.

This study is one of only a few to explore the incidence of MRH in a population of older adults recently discharged from hospital, and highlights a significant problem both in terms of the extent of MRH, and the impact on patients and on healthcare provision. Arguably this is a situation that is going to intensify as a multimorbid population ages, but in this study, and others[2,14,85], it appears to be preventable in some cases, and so steps need to be taken to mitigate this risk. It is difficult to compare the incidence of MRH reported in this study to previous research due to the small number of studies focussing on older adults during the post-discharge period, and the significant heterogeneity in study design which has resulted in a varied incidence (14-46%), as reported by Garcia-Caballos and colleagues in a review of the literature.[24] That being said, the incidence in this study is higher than that reported in the wider MRH literature, and is similar to those post-discharge studies where the incidence reported was at the higher end of the range. This is most likely due to the level of frailty in the study population.

Inconsistency was found across the literature regarding which variables are associated with MRH; the one exception being the number of medicines, where although the effect size varies depending upon the handling of the data during analysis, the association was strong and independent of other factors, as found in this study. Hand grip and nutritional status, both considered to be markers of frailty, demonstrated significance at univariate level, and with very little previous research exploring their association with MRH, further investigation is required to confirm these findings.

Where previous studies have focussed on co-morbidities and medicine related variables, this study highlighted the importance of considering a broader range of variables including those

relating to the support mechanisms around how the medicines were used outside of the hospital, and the robustness of systems aimed at optimising outcomes. This broader consideration can be seen with the case of an 88 year old gentleman with atrial fibrillation, prescribed warfarin for the primary prevention of stroke but spending sub-optimal time in the therapeutic range. Whilst his labile INR may have been the consequence of age-related increased sensitivity to warfarin[237], in this case the patient had difficulty remembering to take his warfarin, and so a system was devised between the patient and his regular carer to assist adherence. This system worked well until the carer was admitted to hospital, resulting in a change to the support system and a subsequent re-admission for the gentleman with a cardio-embolic stroke and a sub-therapeutic INR following missed doses of warfarin. The high-risk nature of the medicine in this case example is unquestionably important and illustrates the value of considering the more traditional risk variables, however it is proposed that the psychosocial elements of the case were fundamental in establishing a suitable equilibrium between risk and benefit. Further exploration of psychosocial variables is therefore important to improve our understanding of their influence on MRH.

The conceptual framework (Figure 3.3) developed within this research programme goes some way in capturing the relationship between physiological and psychosocial factors and their influence on MRH, but perhaps not in their entirety. Elements of the psychosocial aspects such as mood and support were explored, and their influence upon MRH was upheld in part by some of the analysis, however further work is required to confirm these relationships. The impact of socioeconomic status, for example, on the patient's ability to avoid or cope with MRH also requires exploration.

The conceptual framework does not capture the changing nature of an older person's vulnerability. The dynamism of the risks and protective systems is evident, as illustrated in the case earlier where social support appears to have been the keystone to modifying MRH risk. In this study those within institutional care were less likely to experience MRH than those who were at home and heavily dependent upon a package of care. Having a higher risk of MRH however may be an acceptable consequence for some patients if it enables "independent" living within their home environment. Further development of the framework needs to capture the complexity of patient choice with regards to the risk of MRH and potential strategies for moderation.

The conceptual framework places MRH alongside other geriatric syndromes such as falls and incontinence, that is, MRH may be considered one of the "multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render (an older) person vulnerable to situational challenges."[238] In the same way that a fall may be the result of a specific overwhelming event such as a cardiac dysrhythmia, but is more commonly in older people the result of the combination of several factors such as cognitive impairment, gait dyspraxia and a new environment, MRH may also be the result of an specific overwhelming event such as prescription error but is more often the result of receiving a medicine for a reasonable indication, at a reasonable dose but by a patient with impaired physiological and/or psychosocial reserve to withstand a generally low risk but recognised adverse effect. The diversity of systems involved explains, to some extent, the limited predictive ability of any individual risk variables researched in this study and the multicollinearity identified suggests complex interplay between the variables. The dynamic situation with altering vulnerability in both physiological (e.g. acute illness) and psychosocial (e.g. carer holiday) domains means that when trying to predict the likelihood of MRH considering the mere presence or absence of a risk factor may be too simplistic.

## 6.2 Implications of this research

This research has some key implications for the future management of MRH in relation to research, service development and education. Firstly, from a research perspective, a better understanding of what is meant by MRH is required, starting with the definition applied. In this study, MRH was a new term derived by a team of international experts as previous definitions were too narrow or too broad. The development of a new term may be deemed unhelpful, however it aimed to capture two of the frequent types of harm seen in clinical practice, harm from an ADR and non-adherence to medicines. Further work needs to be conducted to determine a term that is universally acceptable in both the academic and clinical arenas.

Consistent and robust measurement and classification of MRH is required to facilitate reliable identification and standardised documentation within the research and clinical environment. At present causality assessments only focus upon ADRs and whilst they may reduce assessor disagreement, they are unable to quantify the contribution that a specific medicine made to the event or prove that there was a connection between the medicine and the event.[239] Thus their

key role is to act as a guide to classifying the likelihood of a relationship between a medicine and an ADR. Considering MRH as a geriatric syndrome (for which polypharmacy is a significant risk factor but not the actual problem) may facilitate it's formal classification as seen with the establishment of formal criteria to define other syndromes e.g. the use of the Diagnostic and Statistical Manuals for the classification of psychiatric disorders[240], and so allow comparison of studies and pooling of results. Standardisation of causality assessments, outcome definitions and preventability measures that have clinical utility are therefore required to facilitate high quality and valuable translational research of MRH in frail older adults.

When considering MRH there is a need to embrace the environment in which the medicine is used and the factors which influence its use and the patient's response. This is likely to be complex, and where previous studies have mainly focussed on MRH within the hospital or causing hospitalisation, future research needs to be multi-sector with an emphasis upon the transitions of care, a particularly high-risk stage in care for older adults[23,215]. The association of MRH with low hand grip, impaired nutritional status, depression, use of a MCA, multimorbidity and a high number of medicines suggests that patients with deficits across multiple domains are at an increased risk of experiencing MRH. Further research is required to confirm these findings, and the study of potential interventions to reduce the risk of MRH should focus on the modification of these risks where possible.

Secondly, from a service development and delivery perspective, the high incidence of MRH in frail older adults identified in this study suggests that it should be expected and considered as one of the differential diagnoses when an older adult taking medicines presents with a new symptom. Two challenges are how to capture such data, and how to utilise it to inform and improve local practice. As observed during the study, when patients were re-admitted with potential MRH the medicine would be altered, but it was infrequently documented as the cause or a contributor to the clinical condition of the patient. ICD 10 codes are available for ADRs but they are many, 827 were identified in a systematic review of the medical literature, and there is great variability in their use[241]. Consensus on the most appropriate codes to use, and the development of clinical standards incorporating recommendations for the accurate documentation of MRH, may facilitate future audits of practice and inform service improvement strategies.

Any service improvement strategy relating to MRH must recognise that it is a problem that transcends both health and social care services, and therefore interventions must reach beyond the limits of healthcare practices to incorporate social care. The package of care was important not only with regards to the likelihood of a patient experiencing MRH, but also in how the patient responded to harm. The individuals responsible for the delivery of this care however receive very little training in the recognition or management of MRH. Educating social care staff in the identification of those at risk, and providing a clear referral pathway may not prevent MRH, but could help in the early management of harm with a consequential reduction in severity.

Where previous systems to identify and manage the risk of MRH have focused on prescribing criteria such as STOPP/START, thus providing a one-dimensional approach; new systems that consider the complexity of MRH and the importance of psychosocial variables in addition to the more traditional variables could better mitigate the risk of MRH. Clinical pharmacists within general practice are ideally placed to advance the identification and management of risk through referrals from concerned patients, carers and health and social care workers; improved monitoring of medicines[242] and; the development of personalised care plans, an intervention which has demonstrated improved outcomes for patients with long term conditions[243]. This form of individualised complex review, whilst time-consuming, considers the potential risk of MRH in a much broader context than looking at the medicines alone. This could help us move away from the MCA style blanket intervention, which from the findings of this study, and others[233,234], does not universally support adherence and may, for some patients, increase the risk of MRH. However, for this to be achieved, MRH needs to be recognised as a priority and the resources necessary to develop and target interventions need to be made available.

The MRH risk prediction model of the future needs to be a “live” system in order to capture a patient’s risk as it changes over time, and so minimise harm early through communication with multiple agencies across health and social care, and link to a referral system where red flags alert staff to potential MRH. Advancement in information technology brings such interventions within reach and the outcomes of the SENATOR Project[147], a pan-European collaboration which aims to develop and test a new software engine for the optimization of medical and non-drug therapy in older people with multimorbidity and polypharmacy, are eagerly anticipated. The aim of this software is to provide non-specialist clinicians with evidence-based recommendations using a number of validated resources: STOPP/START (to identify potential inappropriate prescribing),

SafeScript (a database of drug-drug interactions), British National Formulary (a database of licensed indications), Cumulative Illness Rating Scale for Geriatrics (CIRS-G) to calculate the risk of death in the next year) and a tool to predict the risk of ADR. The ADR risk prediction component will use either the GerontoNet model[114], described earlier in this thesis in the systematic review, or a new prediction model developed by the research team, with selection based upon model accuracy. The output of the software will be a bullet-point list of recommendations that the authors recognise will require clinical judgement, in conjunction with the patient, to determine the appropriate actions to take. This software package commendably incorporates both process-based interventions such as appropriate prescribing criteria, and a prediction model to identify those patients most at risk, in addition to targeting generalists who have the greatest contact with the high-risk older population but with minimal specialist training. It is not yet known which ADR risk prediction model will be integrated into the software but should it be the GerontoNet model[114] then the psychosocial variables that may be an important component of identifying older adults at risk of MRH will be absent, bringing in to question the value of this system.

When considering the implications of this research on education, geriatrics has not been a strong feature of medical or pharmacy training and a change in approach is required that extends beyond these two professions across the multidisciplinary team. A qualitative analysis of 22 doctors in Ireland identified that a specific lack of geriatric pharmacotherapy training at an under and postgraduate level was a reason why potentially inappropriate prescribing occurs.[244] Doctors were selected using a sampling matrix to ensure representativeness across grade (from 1st year qualified to consultant level); area of practice (10 were practicing in geriatrics and 12 in general medicines); and type of hospital where they work (large and small, public and voluntary/private hospitals). They commented that although experiential learning is how they develop their prescribing skills, more specific structured training is also required as "there is no distinction made between older patients and the general adult population".[244] The Silver Book[245], whilst focussing on urgent care needs of older adults, makes recommendations that are applicable outside of the emergency department, describing key skills and competencies, training and development for doctors, nurses, physiotherapists and occupational therapists. The authors also recommend that additional training should extend to health care agencies, social services and community teams, and should preferably be undertaken jointly. Positive outcomes have been reported from inter-professional education (IPE)[246] in the care of older people and so this would seem to be a valuable

approach. The Older Persons' Fellowship at King's College London, sponsored by Health Education England, provides such a learning opportunity for senior nurses and allied health professionals working in older people's services across England, with the aim of developing specialists and future leaders. In accordance with the findings from this thesis that the risk factors for MRH extend beyond the patient's comorbidities and medicines, education needs to extend beyond geriatric pharmacotherapy in order to equip health and social care professionals with the skills required to identify MRH and the associated potential risks.

Unlike the medical and allied health professional, guidance for pharmacy education focussing on the care of older people appears to be lacking. At an undergraduate level, pharmacy teaching often focuses on the single disease model with the development of clinical knowledge driven by guideline-based recommendations as opposed to the underpinning science. In a complex older population where evidence-based medicine is limited, and multimorbidity common, making treatment recommendations is dependent upon the ability to work from first principles. Furthermore, the lack of education around the psychosocial influences on how medicines are used and the impact of an individual's health beliefs on adherence and the risk of MRH need to be addressed. At a postgraduate level, these skills need to be maintained, which some academic clinical pharmacy programmes achieve, however these tend to be aimed at hospital pharmacists. Community pharmacists, whose daily workload will frequently involve interactions with complex older adults and their carers through the supply of medicines for long-term conditions, are not adequately catered for.

Clinical pharmacists in GP practices will need to be knowledgeable in the intricacies of geriatric pharmacy as a substantial proportion of their work is likely to focus on the review of complex and potentially frail older adults. A useful professional curriculum developed by the Royal Pharmaceutical Society Faculty, with the support of the UK Clinical Pharmacist's Association and endorsed by the British Geriatrics Society is available, but is aimed at those practicing at an advanced level, leaving a gap in the training of those beginning to consult within general practice. This research calls for consultant pharmacists with expertise in the care of older people, and an understanding of the complex interaction between health and social care, and physiological and psychosocial risk variables for MRH, to support and advise the development of a curriculum which incorporates the management of medicine in older adults at all stages of a pharmacist's career.

The incidence of MRH and associated costs[2,247], especially in the older population (which is the fastest growing segment of society[248]), would suggest that MRH should become one of the public health priorities for the country. Adequate resources may then become available to tackle the challenge of polypharmacy, multimorbidity and the accompanying MRH from a research, service development and educational perspective.

## 6.3 Future work

This study identified a high incidence of MRH and several variables, some not previously investigated in relation to MRH, which potentially increase the likelihood of MRH in a frail older population following an acute hospital admission. It also suggests that MRH risk needs to be considered in the context of impaired physiological and psychosocial systems. These findings need to be confirmed in a larger population where we need to ensure the adequate blinding of those classifying the final outcome, and the use of standardised definitions.

Of primary importance with regards to future work in the area of MRH in older adults is the need to gain international consensus on clear definitions. This work would include definitions for the preventability and severity of harm due to medicines, and classification strategies that are reproducible and applicable across research and clinical practice. There are many causality assessment tools available in the literature, each with advantages and disadvantages[249] but none of which are validated in older adults or used routinely in clinical practice. They are arguably not appropriate for modern clinical research, especially those measures which incorporate a medicines re-challenge or use of placebo, such as the Naranjo algorithm. This algorithm also does not allow for drug-drug interactions to be the cause of ADRs which is problematic in an older population where polypharmacy is common, and the potential for drug-drug interactions high. The involvement of subject area experts from healthcare, social care and research sectors, using a process such as a Delphi technique, may help to develop suitable definitions and assessment criteria and so increase the value of further research in the area.

This study proposed MRH as a geriatric syndrome. Merely exploratory in nature, it did not intend to demonstrate any cause and effect, and before causal pathways can be researched further, work is required to establish the associations between both psychosocial variables as well as those which are predictive of geriatric syndromes. Further analysis of the data collected for this

study could have been conducted, however this would have been post-hoc “fishing” subject to over interpretation. A future research study should expand upon the hypothesis-generating work conducted here using a larger patient sample, and in a population with varying degrees of frailty, measured and sampled in a more robust manner.

To further test the conceptual framework, expansion of the work conducted by Cullinan and colleagues[156] to determine if a FI could identify those at risk of MRH in the outpatient setting is recommended. The implementation of the electronic FI within general practice and the utilisation of clinical pharmacists in general practice to identify post-discharge MRH during medicines reviews could facilitate such a study. The associations of the FI with MRH should be compared to routine clinical judgements of doctors and pharmacists in order to determine any superiority in terms of predictive ability.

Research into appropriate interventions to reduce MRH should be attempted however it is important that the dynamic nature of frailty, and thus MRH, is considered as it is unlikely that a single intervention, at a single point in time will prove to be effective. As the only consistent predictor of MRH, the starting point for interventional research may focus around managing polypharmacy and embracing comprehensive medicines reviews, which incorporate the concept of deprescribing, as part of individualised care planning. The risk versus benefit of particular medicines for each patient is likely to change over time, and so an exploration of the most appropriate frequency for review is also required.

Due to the lack of involvement of older adults in clinical trials, data pertaining to the benefit of commonly prescribed medicines is little known in this population. Future studies using big data (such as HES data) may help to develop an understanding of the benefits by reporting numbers needed to treat (NNT), but understanding the risk benefit ratio is likely to be more challenging. The risk of harm from medicines in older adults needs to be considered at an individual patient level due to the complexity of MRH. Therefore, if a true risk benefit analysis is to be undertaken then we need to focus on the likely benefits of treatment for that specific older patient, so that the risk can be judged against this. Furthermore, for research at a population and individual patient level, appropriate outcome measures need to be defined; where increased survival may be perceived as an optimal outcome by a clinician, this may not be the priority of an older patient.

Adopting this patient focussed approach may ultimately reduce the number of medicines an older person is prescribed and so reduce the risk of MRH.

As identified in previous work[215], and observed in this study, poor communication across the healthcare interface can contribute to MRH and so reviewing the system-based challenges which hinder good communication between care settings and care teams is required. Where appropriate, this may involve supporting the patient to become the custodian of information about their medicines through use of, for example, a medication passport[250]. It will be necessary however to recognise that the patient themselves may not always be the most appropriate recipient of information. As was identified in this study, patients are often not responsible for their medicines. Identification of the most suitable person to communicate with regarding medicines-related information is important, especially at a time of great change such as hospital discharge. A recent study found that informal caregiver integration during the discharge planning of older adults reduced hospital re-admission.[251]

Finally, an exploration of the potential utilisation of future technologies may transform the way in which medicines and their associated risks are managed. We are now living in the connected age where the internet of things, (the interconnection via the internet of computing devices embedded in everyday objects thus allowing them to send and receive data and therefore be controlled remotely), is rapidly expanding. Industry leaders, such as Nokia, have identified the potential financial gains to be made from the healthcare market and support the development of assisted living technologies. An example of a connected assisted living device is the Pivotell compliance aid which can dispense pills up to 24 times a day and notify a designated contact via email, or text, if a scheduled dose has not been removed[252]. Experts in the care of older people may immediately see potential flaws with such a system. It is therefore crucial that they engage with technology developers to facilitate maximum gains for the patient and health and social care systems from industry investments, and to ensure such interventions are adequately researched prior to widespread implementation.

## 6.4 Conclusion

Deficits in both physiological and psychosocial systems are contributors to the likelihood of MRH, as are the protective mechanisms which are employed by care givers, health professionals and the patient themselves. As a consequence, significant variability exists within this population and the clinical nuances of age heterogeneity may not permit the use of risk prediction in this population. The House of Lords criticised the preparedness of the health service to cope with an ageing population.[44] To address this criticism, instead of striving to develop predictive models, the emphasis should be placed upon identifying those who are vulnerable to adverse events and developing individual treatment plans which not only meet the inter-individual variability but the intra-individual variability of risk that is presented over time. Focussing on medicines related harm, and changing the approach taken to the prescribing and review of medicines is required. This study confirms the potential harm that medicines can cause in older patients and therefore they need to be considered as a potential part of the clinical problem and not always solely the solution.

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# Appendix A. Publication of systematic review

Clinical Interventions in Aging

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ORIGINAL RESEARCH

# Predicting adverse drug reactions in older adults; a systematic review of the risk prediction models

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**Abstract:** Adverse drug reaction (ADR) risk-prediction models for use in older adults have been developed, but it is not clear if they are suitable for use in clinical practice. This systematic review aimed to identify and investigate the quality of validated ADR risk-prediction models for use in older adults. Standard computerized databases, the gray literature, bibliographies, and citations were searched (2012) to identify relevant peer-reviewed studies. Studies that developed and validated an ADR prediction model for use in patients over 65 years old, using a multivariable approach in the design and analysis, were included. Data were extracted and their quality assessed by independent reviewers using a standard approach. Of the 13,423 titles identified, only 549 were associated with adverse outcomes of medicines use. Four met the inclusion criteria. All were conducted in inpatient cohorts in Western Europe. None of the models satisfied the four key stages in the creation of a quality risk prediction model; development and validation were completed, but impact and implementation were not assessed. Model performance was modest; area under the receiver operator curve ranged from 0.623 to 0.73. Study quality was difficult to assess due to poor reporting, but inappropriate methods were apparent. Further work needs to be conducted concerning the existing models to enable the development of a robust ADR risk-prediction model that is externally validated, with practical design and good performance. Only then can implementation and impact be assessed with the aim of generating a model of high enough quality to be considered for use in clinical care to prioritize older people at high risk of suffering an ADR.

**Keyword:** aged, stratified care, prognosis, medication-related harm

## Introduction

Adverse drug reactions (ADRs) have long been recognized as a potential outcome of taking medicines, and while the severity of such reactions may vary, a significant proportion of ADRs are responsible for hospital admissions.[1] Investigators have strived to identify the key factors that increase a person's risk of suffering an ADR, especially in older adults, a group nearly seven-times more likely to be hospitalized due to an ADR when compared to younger people.[2]

We know that the changes in drug pharmacokinetic and pharmacodynamic properties that occur as a result of the aging process often lead to an increased susceptibility to ADRs.[3] Polypharmacy, a frequently reported risk factor for ADRs,[4] is on the increase as people live longer with multiple chronic conditions, so stratifying an older patient's risk of suffering an ADR might be attractive.

Risk prediction is a routine component of everyday medicine in both specific areas (for example, approaches used to determine stroke risk in patients with atrial fibrillation)[5] as well as more generally, to identify patients at risk of hospital admission.[6] ADR risk stratification in older adults could assist in case prioritization, supporting

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clinicians and patients to make informed decisions about treatments and for the delivery of a more efficient health care service.

Accurate risk prediction models are the result of four key stages: development, validation, impact, and implementation.[7] It is recognized that often only the first two stages (ie, development and validation) are completed, the methods and outcomes of which are often poorly reported.[7] Furthermore, to be of practical use, these models should use clearly defined easily obtainable data, have good predictive power, be tested in a large sample representative of the target population, and have high reliability and face validity.[7] A recent systematic review emphasized that failure to consider risk prediction in a clinical setting can result in poor care.[8] With regard to the prediction of medication risk in older adults, as no systematic review of this area has been undertaken, we aim to identify and assess the quality of validated ADR risk-prediction models for use in adults over 65 years of age in order to determine their potential benefit to clinical practice.

## Method

### Information sources and search

A systematic search for published material was performed, up to November 30, 2012, using standard databases (Embase, Medline, Cochrane Library, BNI, CINAHL, NeLM, IPA) to identify relevant studies as well as those associated with policy documents and unpublished work (Department of Health, King's Fund, Worldcat, Open Grey, Google Scholar). For the key studies, the bibliographies and citations were reviewed, and an author search was performed, to identify any additional studies.

Our search strategies for each database included no restrictions and used standard terms based around three key concepts: older people; medication-related problems; and clinical prediction models. The full Embase search strategy is provided in Table S1.

### Inclusion criteria and selection

Two researchers (JMS and SDE) independently screened titles, abstracts, and, where necessary, full texts in order to identify studies that potentially satisfied the following inclusion criteria:

- Majority of patients ≥65 years old
- Included patients who experienced an adverse drug event (ADE) or ADR but excluded prescription errors
- A multivariable approach in design and analysis was followed
- The model had been validated.

### Data extraction

Data were extracted (by JMS) to provide details of the population characteristics, study design, process of model development and validation, and performance of the model, as presented in Tables 1 and 2. This was confirmed by secondary reviewers (SDE and ATP) and, where disagreement occurred, this was resolved through discussion.

### Quality assessment

All papers were initially reviewed (SDE and JMS) using a standard approach for developing and testing clinical prediction models to satisfy a range of criteria representing four stages: development (identification of candidate predictor variables and model design); validation (testing the performance of the model); impact (measurement of usefulness in the clinical setting); and implementation (widespread acceptance and adoption in clinical practice).[7]

As no standardized quality assessment for risk-prediction models is available, each study was analyzed using criteria derived from the published literature.[8–11] Candidate predictor variables were grouped into three categories to allow for comparison between studies: demographic factors; medical factors (eg, comorbidities); and medication factors (eg, class of medicine). Event rate was calculated as percentage ADR/ADE rate where it was not reported by the authors in this form. Quality of design and reporting of the studies was compared based on ability to comply with the standard criteria (Table S2). The overall performance of the models was determined by review of their accuracy, discrimination, and calibration through internal or external validation, as described in detail in Table S2.

## Results

A total of 13,423 potentially relevant titles were identified from the literature, of which only 549 were associated with adverse outcomes of medicines use. The majority of these (535) were excluded on review of their abstract as they were not associated with the design of a risk prediction model; many of these were observational (see Figure 1). Full papers were requested for the remaining 14 articles for further scrutiny, and four met the inclusion criteria and were subjected to a full evaluation.[12–15]

### Excluded papers

The 535 articles excluded could be categorized into observational studies (325), those in which indicators to support quality prescribing were developed (63 studies; for example Beers' criteria[16]), and those applying the prescribing indicators (147 studies) to determine any association between inappropriate medicines and adverse outcomes.

**Table 1** Summary table of population characteristics of included studies

| Author | Development | | | | | | Validation |
|---|---|---|---|---|---|---|---|
| | Population and setting | Number of patients (n) and common comorbidities (%) | Number of drugs | Primary outcome measure and rate | Drugs most frequently associated with primary outcome (%) | Most frequent body systems affected by ADRs (%) | Population and setting |
| McElnay et al[12] | Age: 65–98 years<br>Location: acute hospital (UK)<br>Year: NR<br>Sex: F 49.5%<br>Ethnicity: NR | n=929<br>Comorbidities not reported | Mean: 4.3 (range: 1–15) (SD: NR) | ADE – ADR and adherence 16% | Digoxin<br>ACE inhibitors<br>Antidepressants<br>Insulin | NR | n=204 (number ADRs unknown)<br>Cohort similar to development cohort |
| Tangiisuran[13] | Age: 85±7.9 years<br>Location: acute hospital (UK)<br>Year: 2007 and 2008<br>Sex: F 61%<br>Ethnicity: white | n=690<br>HTN (73)<br>Infection (44)<br>Anemia (41)<br>MSK (41) | Mean: 7 (range: 5–10) (SD: NR) | ADR 12.5% | Cardiovascular (34%)<br>Analgesics (16%)<br>Antidiabetics (13%)<br>Antibiotics (13%) | GI (21.1%)<br>CV (20%)<br>Neuropsychiatric (14.7%)<br>Endocrine (13.7%)<br>Metabolic/renal (11.6%) | n=483 (56 suffered ADR)<br>Number of drugs 11.0±7.0<br>Cohort similar – drawn from four European countries (UK, Belgium, Italy, and the Netherlands) |
| Onder et al[14] | Age: 78±7.2 years<br>Location: acute and community hospitals (Italy)<br>Year: 1993–1997<br>Sex: NR<br>Ethnicity: NR | n=5936<br>HTN (24)[31]<br>CHD (21)[31]<br>Diabetes (16)[31]<br>COPD (14)[31]<br>CVD (13)[31] | Mean: 6.3 (range: NR) (SD: 3.6) | ADR 6.5% | Antineoplastics (19.5%)[31]<br>NSAIDs (5.2%)[31]<br>Antipsychotics (4.4%)[31]<br>Antibiotics (3.9%)[31]<br>Corticosteroids (3.3%)[31] | GI (18%)<br>CV (25.3%)<br>Neuropsychiatric (17.8%)<br>Dermatologic (11.7%) | n=483 (56 suffered ADR)<br>Number of drugs 11.0±7.0<br>Cohort similar – drawn from four European countries (UK, Belgium, Italy, and the Netherlands) |
| Trivalle et al[15] | Age: 83.6±7.9 years<br>Location: 16 rehabilitation hospitals (France)<br>Year: NR<br>Sex: F 72%<br>Ethnicity: NR | n=576<br>CV (72)<br>MSK (48)<br>GI (36)<br>GU (29)<br>Neuro (26) | Mean: 9.4 (range: NR) (SD: 4.24) | ADE 39% (not all were included in the study) | Psychotropics (23%)<br>Antihypertensives (17%)<br>Anticoagulants (14%)<br>Analgesics (13%) | GI (25%)<br>Biological abnormalities (22%)<br>Other (20%)<br>Neuropsychiatric (12%) | *Secondary study*[21]<br>n=513 (135 ADRs)<br>Number of drugs 7 (IQR 7–10)<br>Cohort similar to development cohort – drawn from Republic of Ireland<br>Bootstrapping<br>n=NR<br>Validation cohort similar to developmental cohort |

**Abbreviations:** ACE, angiotensin converting enzyme; ADE, adverse drug event; ADR, adverse drug reaction; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cerebrovascular disease; F, female; GI, gastrointestinal; GU, genitourinary; HTN, hypertension; IQR, interquartile range; MSK, musculoskeletal; Neuro, neurological comorbidity; NR, not recorded; NSAIDs, non-steroidal anti-inflammatory drug; SD, standard deviation.

Table 2 Summary of quality assessment of included studies

| Standard criteria | | McElnay et al[12] | Tangiisuran[13] | Onder et al[14] | Trivalle et al[15] |
|---|---|---|---|---|---|
| Study design | | Prospective cohort (development and validation) | Prospective cohort (development and validation) | Retrospective cohort (development)<br>Prospective (validation) | Prospective cohort (development)<br>Retrospective cohort (validation) |
| Participant recruitment | Clear inclusion criteria | Yes<br>Development<br>– Nonelective admissions<br>– Medical, surgical, cardiac and geriatric, wards in a single hospital<br>– >65 years old<br>– Taking medicines<br>Validation as above | Yes<br>Development<br>– Admitted to one of four care of the elderly wards in a teaching hospital<br>– >80 years old<br>Validation<br>– Admitted to one of four European hospitals<br>– ≥65 years old<br>– Taking medicines | Yes<br>Development<br>– Selected community- and university-based hospital admissions<br>– ≥65 years old<br>– Taking medicines<br>Validation as above except admitted to one of four European hospitals | Yes<br>Development<br>– Consecutive admissions to 16 geriatric rehabilitation centers<br>Validation as above |
| | Evidence that patient selection was not biased | Unsure<br>Data only collected from 50% of development-phase and 42% of validation-phase patients recruited who underwent interview | Yes<br>All patient exclusions were for appropriately assessed reasons | Unsure<br>An unknown number of patients were excluded due to incomplete data<br>61 cancer patients excluded | Unsure<br>Data from 71 patients were excluded (these patients were either part of an intervention arm or not present for the whole 4 weeks of the study) |
| | Acceptably low rates of loss to follow-up | Yes<br>Data from all patients who underwent interview were used in development and validation of model | Yes<br>No patients lost to follow-up | Yes<br>No patients lost to follow-up | Yes<br>No patients lost to follow-up |
| | Clear methods used to measure predictors | Partly<br>2/7 identified variables were not easily quantifiable (ie, "GI problems" and "patient thinks drugs are responsible for hospital admission") | Mostly<br>Data on 17 potential variables assessed<br>Not clear how comorbidity, liver disease, previous history of ADR, or known allergy to medication were defined | Partly<br>A trained physician completed a questionnaire for each patient, but unclear how key variables (comorbid conditions, liver disease, previous ADR) were defined or consistently applied between assessors | Partly<br>Where candidate predictors were reported, they could be clearly described<br>Potential candidate predictors that were not included in the model are unknown |
| | Blinding to outcome | Yes<br>Data collected prospectively | Yes<br>Data collected prospectively | Partly<br>Blinding is not reported for the development phase<br>Physicians collecting data for the validation phase were blinded | Yes<br>Data collected prospectively |
| | Conformity with linear gradient | Not reported | Not reported | Not reported | Yes<br>Linearity was checked where possible |

| | | | | | |
|---|---|---|---|---|---|
| | Test for colinearity | Partly<br>Outlined in method but not mentioned in results | Partly<br>Outlined in method but not mentioned in results | Not reported | Yes<br>High-correlation risk factors were identified and examined in separate models |
| Outcome[b] | Appropriate methods used to measure outcomes | Partly<br>Data sourced from patient records and interviews<br>ADE as defined by:<br>– ADR (measured using modified Naranjo scale)<br>– Adherence (self-reported) | Partly<br>Medical information and health care staff reviewed daily using standardized checklist<br>Suspected ADRs assessed for causality, preventability, and severity using Naranjo algorithm, Hallas criteria, and a confidence in causality Likert scale | Partly<br>Wards visited daily, and nursing and medical records examined daily<br>Causality was assessed based on Naranjo algorithm | Partly<br>A combination of approaches used to identify ADEs: a self-generated standardized 32-item checklist was completed by nursing staff. Incident reporting and weekly chart review were also conducted. Four criteria were used to assign likelihood of causality<br>Not possible to determine |
| Statistical power | Sufficient events per variable (ie, >10) | No<br>Unable to determine exact number, but <10 | No<br>86 ADRs/34 candidate predictor variables =2.5 | Yes<br>Unable to determine exact number but >10 | |
| Selection of predictor variables | Method of selection reported for independent variables | Partly<br>Screened in univariate analysis and entered into model if $P<0.25$<br>Applicable to >5% of population | Yes<br>Screened in univariate analysis and entered into model if $P<0.05$<br>Variables identified from other studies entered into model if $P<0.25$<br>Applicable to >5% of population | Yes<br>Screened in univariate analysis and entered into model if $P\leq0.10$ | Yes<br>Screened in univariate analysis and entered into model if $P<0.05$<br>Applicable to >5% of population |
| | Fitting procedure reported | Yes<br>Stepwise backward-elimination procedures (using maximum likelihood method)<br>Preliminary removal of variables at $P=0.15$ then $P=0.05$ | Yes<br>Multivariate logistic regression using backward-elimination procedure and forward selection<br>Removal criteria $P=0.10$ | Partly<br>Stepwise logistic regression<br>Added and retained variables if $P\leq0.1$<br>Methods of variable elimination and retention were unclear | Partly<br>Stepwise logistic regression<br>Retained variables if $P<0.05$<br>Methods of variable elimination and retention were unclear |
| Model performance | Development phase reported | No | Yes<br>Discrimination as AUROC reported with CI<br>Calibration as Hosmer-Lemeshow and Nagelkerke $R^2$<br>Sensitivity and specificity reported | Partly<br>Discrimination as AUROC reported with CI<br>Sensitivity and specificity reported | No |
| | Validation phase reported | Partly<br>Only overall accuracy, sensitivity, and specificity reported | Yes<br>Discrimination as AUROC reported with CI<br>Sensitivity and specificity reported | Partly<br>Discrimination as AUROC reported with CI | Partly<br>Discrimination as AUROC reported with CI |

**Notes:** [a]Interactions and coding were not dealt with in any of the studies. [b]All studies collapsed continuous categorical data into binary outcomes.
**Abbreviations:** ADE, adverse drug event; ADR, adverse drug reaction; AUROC, area under the receiver operator curve; CI, confidence interval; GI, gastrointestinal.

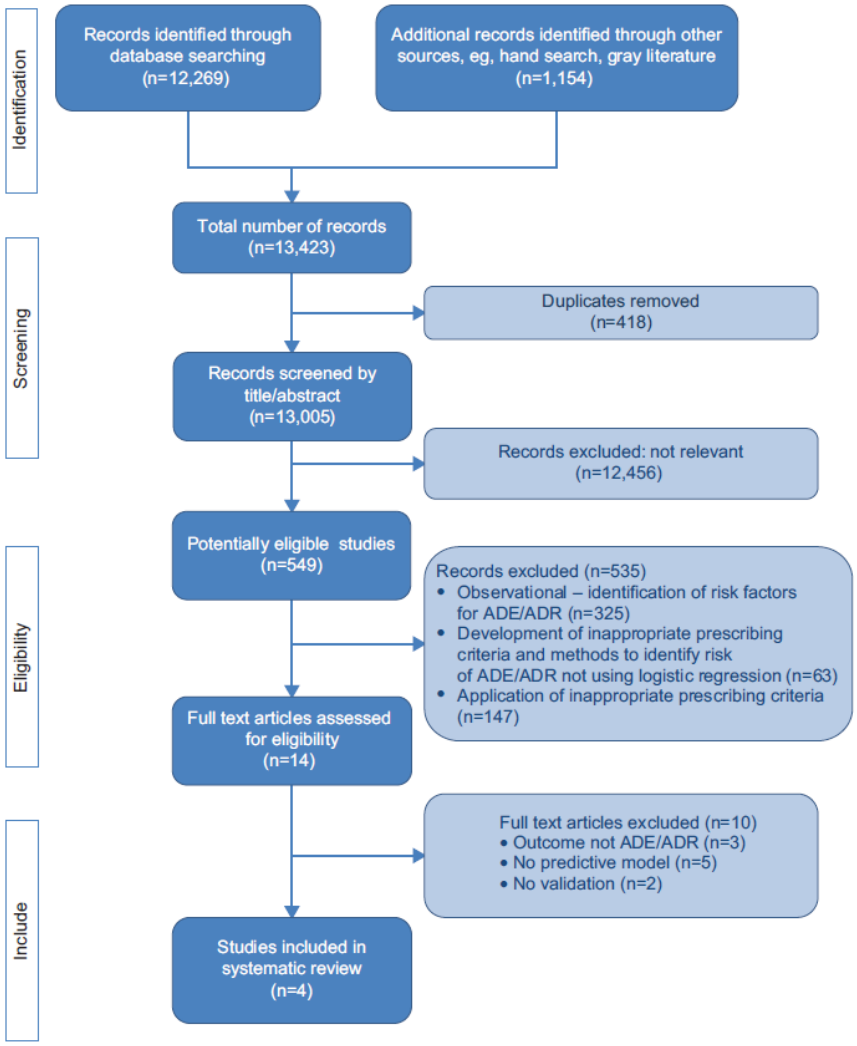


**Figure 1** PRISMA[32] flow diagram.
**Abbreviations:** ADE, adverse drug event; ADR, adverse drug reaction.

## Included papers

### Population characteristics

All included studies were conducted in Western Europe, and only in the hospital setting (acute, community, and rehabilitation hospitals) (Table 1).[12–15] Two studies represented the very elderly (aged over 80 years).[13,15] Patient functionality was reported by Onder et al[14] Tangiisuran,[13] and McElnay et al[12] and was measured using patient-perceived health status, Katz Index, and Barthel Index.

The primary outcome in all of the studies was ADR,[17] with one study using ADE synonymously[15] and another[12] including ineffective treatment in an extended definition. The proportion of patients who experienced an ADR/ADE ranged from 6.5% to 39%, with gastrointestinal, cardiovascular, and nervous systems being those most frequently affected. Medications most frequently associated with ADRs/ADEs included psychotropics, anticoagulants, and analgesics.

### Quality assessment – overview

Whilst all models included the development and validation phases, none addressed the impact and implementation phases.

## Model development

### Study design

During the development phase, all except Onder et al[14] used a prospective case-cohort design method, where events accrued over the study period. Onder et al extracted 3 years of data from a historical database, whereas data were extracted over 1–6 months in the other studies. Patient medical notes, in-patient charts, and electronic records were reviewed in the prospective studies.[12,13,15] In addition, McElnay[12] asked a sample of the patients about aspects of their medicines, while Trivalle et al[15] used patient self-reporting as a trigger for further analysis. The validation phase was conducted prospectively for all studies except for that of Trivalle et al where bootstrapping was used.

### Participant recruitment

The criteria for inclusion and exclusion as well as any loss to follow-up were clearly described in all studies, although reporting of patient selection was poor (Table 2). An unknown number of patients were excluded by Onder et al due to incomplete data.[14]

### Candidate predictors

The handling of candidate predictor variables was generally poor. In all studies, the description of the variables was inadequate; where Trivalle et al[15] did not report the potential candidate variables, McElnay et al[12] Tangiisuran[13] and Onder et al[14] used variables with unclear definitions, eg, "previous ADR". Despite being labeled as a "bad idea",[18] dichotomization of continuous candidate predictor variables (eg, four or more comorbidities, more than eight medications, previous ADR) was common practice, and may explain the failure to consider conformity to the linear gradient in all[12–14] but the Trivalle et al study.[15] Interactions were poorly addressed, as was the coding of variables. Insufficient detail in the results made it difficult to establish whether tests that were mentioned in the methods had been implemented; eg, McElnay et al[12] reported testing for interactions and colinearity, but this was not followed through to the results. Predictor-variable measurement was blinded for outcome in the development phase in three of the four studies.[12,13,15]

### Outcome

The occurrence of an ADE/ADR was the primary outcome measure for all studies. A validated assessment of causality, in the form of the Naranjo algorithm[19] or Hallas criteria,[20] was adopted by all but Trivalle et al who used their own checklist.[15] The outcome was recorded in the form of continuous categorical data (ie, unlikely, possible, probable, definite) then collapsed to produce a binary outcome. Possible, probable, and definite were combined as a positive outcome. Blinding to the outcome occurred in all four studies during the validation phase.

### Statistical power

The poor description of potential candidate predictor variables made it impossible to determine if the studies were adequately powered (Table 2).

### Selection of predictor variables

The method of selection of predictor variables for inclusion within the multivariable analysis was described in all of the studies (Table 2). Tangiisuran[13] provided the most detailed description, whilst Trivalle et al[15] provided the least detailed description. Mixed methods (using the literature, expert opinion, and univariate analysis) were used by Tangiisuran.[13] Onder et al appeared to have used univariate analysis alone.[14] There was variation in the significance levels used to retain a predictor variable.[12–15]

### Model performance and validation

The area under the receiver operator curve was used to assess discrimination in three of the four studies, and was 0.70–0.74 for the development phase.[13–15] Sensitivity and specificity were reported by Tangiisuran,[13] Onder et al[14] and McElnay et al.[12] Calibration was only reported by Tangiisuran,[13] for which Hosmer-Lemeshow was satisfactory but Nagelkerke[21] was low.

All models underwent the subsequent stage of validation using a second dataset. Internal validation was reported by McElnay et al[12] and Trivalle[15] in the form of split sample and bootstrapping, retrospectively. External validation was performed by Onder et al[14] and Tangiisuran[13] in the same European cohort. Another research group (O'Connor et al[22]) subsequently applied the model developed by Onder et al[14] providing additional external validation (Table 1). Area under the receiver operator curve in the validation phase ranged from 0.623 to 0.73 (Table 3). The number of patients involved in the external validation ranged from 204 to 483.[12–15,22] Only the study by O'Connor et al[22] met the recommended minimum number of events (100 events and nonevents).

### Score development

Predictor variables within the final models (Table 3) were attributed a points-based score, which was simplified for practical application.[13–15] McElnay et al did not proceed to this stage due to the poor performance of their model.[12]

**Table 3** Summary of final ADR risk-prediction models

| Author | Significant variables in multivariate analysis | Variable coefficient | OR (CI) | Attributed score | Validation |
|---|---|---|---|---|---|
| McElnay et al[12] | Prescribed antidepressants | 1.7569 | 5.7942 (2.12–15.85) | None | Internal (204 patients) |
| | Prescribed digoxin | 0.6884 | 1.9905 (1.05–2.33) | | Accuracy 63.0% |
| | Gastrointestinal problems | 0.7704 | 2.1606 (1.13–4.15) | | Sensitivity 40.5% |
| | Abnormal potassium level | 0.9455 | 2.5740 (1.35–4.91) | | Specificity 69.0% |
| | Thinks drugs were responsible | 1.4375 | 4.2103 (2.18–8.14) | | |
| | Experiences angina | −1.7861 | 0.1676 (0.07–0.42) | | |
| | Experiences COAD | 0.8779 | 2.4057 (1.06–5.44) | | |
| | | −1.0997 (constant) | | | |
| Tangiisuran[13] | Hyperlipidemia | 1.199 | 3.316 (1.811–6.072) | 1 | External (483 patients) |
| | Number of medications ≥8 | 1.194 | 3.300 (1.927–5.651) | 1 | Sensitivity 80.0% |
| | Length of stay ≥12 days | 0.819 | 2.269 (1.345–3.826) | 1 | Specificity 55.0% |
| | Use of hypoglycemic agents | 0.645 | 1.906 (1.040–3.493) | 1 | AUROC 0.73 (95% CI 0.66–0.80) |
| | High white blood cell count on admission | 0.437 | 1.548 (0.940–2.548) | 1 | |
| | | −3.628 (constant) | | | |
| Onder et al[14] (O'Connor et al)[22] | ≥4 comorbidities | Not reported | 1.31 (1.04–1.64) | 1 | External (483 patients) |
| | Heart failure | | 1.79 (1.39–2.30) | 1 | Sensitivity 68% |
| | Liver disease | | 1.36 (1.06–1.74) | 1 | Specificity 65% |
| | Number of drugs ≤5 | | 1 Reference | – | AUROC 0.70 (95% CI 0.63–0.78) |
| | Number of drugs 5–7 | | 1.9 (1.35–2.68) | 1 | External (513 patients) |
| | Number of drugs ≥8 | | 4.07 (2.93–5.65) | 4 | AUROC 0.623 (95% CI 0.570–0.676) |
| | Previous ADR | | 2.41 (1.79–3.23) | 2 | |
| | Renal failure | | 1.21 (0.96–1.51) | 1 | |
| Trivalle et al[15] | Number of medications | Not reported | 1.9 (1.6–2.3) | – | Internal (bootstrap) |
| | 0–6 | | 2.5 (1.5–4.1) | 0 | AUROC 0.70 (95% CI 0.65–0.74) |
| | 7–9 | | 2.0 (1.1–1.37) | 6 | |
| | 10–12 | | | 12 | |
| | ≥13 | | | 18 | |
| | Antipsychotic treatment | | | 9 | |
| | Recent anticoagulant | | | 7 | |

**Abbreviations:** ADR, adverse drug reaction; AUROC, area under the receiver operator curve; CI, confidence interval; COAD, chronic obstructive airways disease; OR, odds ratio.

The score developed by Onder et al[14] was on a points-based system derived from the odds ratio. There was no assessment to determine if any of the predictive ability was lost in this simplification. Tangiisuran[13] assigned one point to each predictor variable based on the "variable coefficient being of the same magnitude". It is unclear how Trivalle et al[15] assigned the values to each predictor variable.

### Impact and implementation

The impact and implementation of these models have not been published, perhaps reflecting their poor to modest performance. McElnay et al recognized the limitation of their level of performance,[12] and both Tangiisuran and Onder et al called for further external validation of their models.[13,14] However, Trivalle et al[15] concluded that their model could be applied in clinical practice alongside other tools, eg, Mini Mental State Exam. It is also worth considering some of the difficulties highlighted by O'Connor et al[22] in the application of Onder et al's[14] model that are due to unclear definition of predictor variables.[14,22] Similar challenges are likely to arise when applying results from Tangiisuran, Trivalle et al and McElnay et al given the poorly defined predictor variables.[12,13,15] The use of variables such as length of stay would also make prospective risk stratification impossible.

## Discussion

Our review suggests that the four models identified, which were designed to predict the risk of older patients suffering an ADR, are not yet suitable for use in clinical practice. While only two (Tangiisuran and Onder et al) were externally validated, their ability to discriminate between those who had experienced an ADR and those who had not was only modest.[13,14] This could result in a failure to identify patients at high risk of experiencing an ADR. Furthermore, none were subjected to the investigational rigor required when producing a risk-prediction model; in particular, none reported the findings of impact and implementation stages, thus widening the gap between research potential and clinical

application. Pressures within health care systems are driving a need for robust clinical risk-prediction models to inform care provision, but, to be useful, these models must be of high statistical quality and be clinically relevant.

All four studies had limitations commonly reported in the prognostic research literature.[7] Three failed to provide sufficient information relating to events-per-variable ratio[12,14,15] and one was insufficiently powered (Tangiisuran),[13] so the risk of a type II error (false negative finding) was more likely.[23] All studies dichotomized their predictor variables (eg, when categorizing the number of medicines) and outcomes (eg, collapsing a continuous ADR causality scale), despite this practice being suboptimal.[18,23] The use of unrepresentative samples and the management of missing data were also problematic, regardless of whether a retrospective or prospective design was used. In addition, there was often a lack of reporting of candidate predictor variables, which could hinder replication by others.[24]

So, if the current risk prediction models have shortcomings, what can we do to limit older adults experiencing ADEs? Although research investigating medication risk in older adults is widespread, the 535 titles identified in our initial search were often associated with other, mainly system-based, approaches to managing risk, and a substantial proportion were observational in nature. This body of evidence documents the complexity of medication risk in older adults and highlights the multidimensional nature of this field, which includes: clinical aspects, such as the changes in drug handling demonstrated in older age; social risk factors, especially during the transfer of care between different settings; and high-risk medicines, where the risk of medicines are considered but not always balanced against the potential benefits. Furthermore, the difficulty in determining whether a patient has experienced an ADR is challenging given the progressive nature of aging, where functional decline and loss of independence are common. Unfortunately, as older adults are often excluded from clinical trials, this limits our understanding of medicine risk in this population, and can result in inappropriate extrapolation of clinical guidelines, often based on research in younger patients.

So, is there a place for risk models in this care setting? A more common strategy is to adopt a systems approach to medicines use where pharmacological appropriateness is monitored, usually by applying a list of prescribing indicators: for example, Beer's criteria.[16] The recognized limitations of such an approach are that it is time-consuming if used in routine care and can be viewed as one-dimensional. This focus on specific medicines often restricts, due to formulary and licensing issues, value in an international context. Perhaps the way forward is a hybrid whereby risk models bring a multidimensional perspective to guide clinical intervention, delivered as part of an integrated system built around the principles of medication safety. If models can map this complex interplay between clinical, social, and medication-related variables to stratify an individual's risk of a future ADE, they may become a useful decision support tool for clinicians and patients to be used alongside systems-based approaches. This approach could help prioritize interventions for those patients at highest risk. Ultimately, the variables associated with medication risk, eg, polypharmacy and renal impairment, are inherent in clinical decisions and form part of a clinician's intuitive risk assessment when prescribing medicines. Furthermore, clinicians often modify decisions based on individual variability, whereas a statistical model may not be able to accommodate the clinical nuances and overcome the gerontological phenomenon of age heterogeneity.[25] While risk prediction models are not intended to replace clinicians' decisions, they should not stratify patients less accurately than clinicians. It would be helpful if future work could compare a clinician's risk stratification against that of an ADR risk-prediction model. This work would help inform the clinical relevance of the model and contribute to the impact and implementation research that is thus far lacking. In the meantime, useful strategies that clinicians may adopt to prevent ADRs occurring are: ensuring that reliable medicines reconciliation is undertaken; avoiding the prescribing cascade (where a drug is prescribed to manage the problem caused by another); and the routine optimization of drug use in line with renal and liver function.

While conducting this systematic review, we could not assess for publication bias using conventional methods such as funnel plots due to the small number of studies available.[26] Publication bias in favor of positive results has been raised as a significant problem in the area of cancer risk-prediction research, and it is likely to be present in this area in which negative results remain unpublished.[27] The proposal to develop reporting guidelines that stipulate registration of all risk-prediction research should go some way in reducing future reporting bias.[28] These guidelines could also be applied to protocols and manuscripts when designing or publishing risk-prediction research, and may be a more suitable tool for quality assessment in the future.[29] In the absence of a consensus guideline, we used an amalgamation of standards for reporting risk-prediction research to carry out this review. This approach should reduce the likelihood of any important quality measures being excluded. In the future, recommendations developed by the Cochrane Prognosis Methods Group

and the Prognosis Research Strategy Partnership should assist investigators in combating the challenges present when conducting risk-prediction research.[23,28,29]

## Conclusion

Risk stratification is attractive, especially in older patients where the population is growing and placing an increased demand on the health care service, a service that is woefully underprepared for the projected global growth to over 2 billion people over the age of 60 years by 2050.[30] We identified four ADR risk-prediction models with poor to modest performance and raised questions about their overall quality, a finding not uncommon in the area of risk-prediction research. If these models are to be embraced as part of routine clinical care, further work needs to be conducted so that external validity can be assured and a practical approach upheld. Only then can implementation and impact be assessed with the view to adoption as part of a systems approach within routine clinical care.

## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary materials

**Table S1** Embase search strategy indicating the order in which the terms were entered and how they were combined

| |
|---|
| **Risk tool** |
| 1. risk assessment.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 2. exp prediction/ |
| 3. exp scoring system/ |
| 4. exp clinical assessment tool/ |
| 5. exp risk factor/ |
| 6. exp risk management/ |
| 7. exp decision support system/ |
| 8. risk stratification.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8[a] |
| **Medication related problem** |
| 10. exp adverse drug reaction/ |
| 11. adverse drug event*.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 12. adverse drug reaction*.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 13. medication related problem*.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 14. drug related problem*.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 15. exp medication therapy management/ |
| 16. drug/ae [Adverse Drug Reaction] |
| 17. exp polypharmacy/ |
| 18. exp medication error/ae, pc [Adverse Drug Reaction, Prevention] |
| 19. inappropriate prescri*.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 20. (readmission and drugs).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 21. patient compliance.mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 22. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21[a] |
| **Elderly** |
| 23. aged/ |
| 24. exp aging/ |
| 25. exp elderly care/ |
| 26. older people.mp. |
| 27. older person.mp. |
| 28. aged over 80.mp. |
| 29. 23 or 24 or 25 or 26 or 27 or 28 or 29[a] |
| **Combined terms** |
| 30. 9 and 22 and 29[a] |

**Notes:** [a]The numbers demonstrate how search terms have been combined ie, all of the terms for the risk tool were combined in Step 9 of the search. Then these combined terms were combined with those from all those relating to medication related problems ie, Step 22 and with terms relating to elderly ie, Step 29. This resulted in a combined search of the terms listed in Steps 9 and 22 and 29.
**Abbreviations:** exp, explode all trees; mp, multiple posting.

**Table S2** Criteria to consider when evaluating the quality of risk prediction models

| Standard criteria[a] | Explanation | Example |
|---|---|---|
| Study design | Prospective: allows optimal collection of potential candidate variables; smaller dataset often generated.<br>Retrospective: enables use of large previously collected datasets; quality of candidate variable data may be compromised due to missing data, which rarely occurs at random. | Prospective study design, n=690, all exclusions were for appropriate reasons.[1]<br>Retrospective study design, n=5,936, unknown number of exclusions due to missing data.[2] |
| Participant recruitment | Inclusion and exclusion criteria should be clearly described to allow full assessment of patient population studied.<br>Any systematic variation in recruitment of patients should be viewed with caution due to risk of sampling bias.<br>There is no predetermined satisfactory number for loss to follow-up; however, it should be considered that missing data impacts on the statistical power of the study. | Interview data was only collected for half of the patients during the development phase.<br>Patients not wishing to participate in the interview may systematically differ.[3] |
| Candidate predictor variables | Variables and their measurement should be clearly defined to allow for replication.<br>Investigators should be blind to outcome to reduce risk of bias.<br>Continuous variables should be assessed for conformity to linear gradient.<br>Not necessary for dichotomous variables; however, dichotomization of continuous variables not recommended as it impacts on the statistical power of the study.<br>Correlation (test for colinearity) between risk variables should be examined and reported. | Unclear how key variables, eg, liver disease, were defined. To replicate, study investigators would be required to apply their own definition, which may have an impact on reproducibility.[2] |
| Outcome | Method of measuring outcome: must be reproducible and, where assessment scales are applied, these should be validated to increase accuracy and reproducibility of the measurement. Dichotomization of continuous outcomes is not recommended as it can affect statistical power. | Investigators generated own causality assessment of unknown validity.[4]<br>Applied widely-used validated causality assessment (Naranjo algorithm).[2] |
| Statistical power | Sample size is calculated based on number of outcome events per variable, where ten events per variable is often recommended. A high number of variables and a rare outcome can result in over-fitting of the model, causing poor generalizability. | Reported 86 ADRs in a sample of 690 patients and assessed 34 candidate predictor variables, resulting in only 2.5 events per variable.[1] |
| Selection of variables | Independent variable selection should be described clearly, and can be based on the literature and/or statistical association as determined by univariate analysis with outcome variable. Selection based upon univariate analysis alone increases likelihood of developing an over-fitted model.<br>Inclusion of variables applicable to over 5% of population may help exclude artifact variables.<br>Fitting procedure (entering of variables into model) should be explicitly stated, including removal criteria. | Variables were entered into multivariate analysis if $P<0.05$ after univariate analysis, or if $P<0.25$ for variables identified from other studies. Liver disease was removed as it applied to <5% of population.<br>Backward elimination and forward selection were used with a removal criteria of $P=0.10$.[1] |
| Model performance | In both development and validation phases, assessment of discrimination and calibration should be reported to determine how well the model distinguishes those who have an ADR from those who have not, as well as how close the prediction is to the observed outcome for that risk group.<br>AUROC >0.7 is often deemed acceptable, but this alone is not sufficient to determine the clinical usefulness of the model.[6]<br>Assessment of the generalizability of the model is important to determine the accuracy of predictions in another population and is recommended prior to routine clinical application. Internal validation, by methods such as bootstrapping (data resampling) or split-sample, assesses how well predictors correspond to the outcome, but leads to optimistic estimates of model performance. External validation is more rigorous and enables assessment of accuracy when the model is applied by investigators not involved in the development of the model. | Discrimination (AUROC) and calibration (Hosmer-Lemeshow) reported in the development and validation phases.[1]<br>Trivalle applied bootstrapping.[5]<br>Onder applied external validation whereby the model was applied by investigators not involved in the development of the model and in a different geographical location.[7] |

**Note:** [a]Criteria derived from the published literature.[8–11]
**Abbreviations:** ADR, adverse drug reaction; AUROC, area under the receiver operator curve.

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## Appendix B. Publication of observational study methods

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BMC Geriatrics

STUDY PROTOCOL Open Access

# Protocol for a Prospective (P) study to develop a model to stratify the risk (RI) of medication (M) related harm in hospitalized elderly (E) patients in the UK (The PRIME study)

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**Abstract**

**Background:** Medication related harm (MRH) is a common cause of morbidity and hospital admission in the elderly, and has significant cost implications for both primary and secondary healthcare resources. The development of risk prediction models has become an increasingly common phenomenon in medicine and can be useful to guide objective clinical decision making, resource allocation and intervention. There are no risk prediction models that are widely used in clinical practice to identify elderly patients at high risk of MRH following hospital discharge. The aim of this study is to develop a risk prediction model (RPM) to identify elderly patients at high risk of MRH upon discharge from hospital, and to compare this with routine clinical judgment.

**Methods/Design:** This is a multi-centre, prospective observational study following a cohort of patients for 8 weeks after hospital discharge. Data collection including patient characteristics, medication use, social factors and frailty will take place prior to patient discharge and then the patient will be followed up in the community over the next 8 weeks to determine if they have experienced MRH. Research pharmacists will determine whether patients have experienced MRH by prospectively reviewing records for unplanned emergency department attendance, hospital readmission and GP consultation related to MRH. Research pharmacists will also telephone patients directly to determine self-reported MRH, which patients may not have sought further medical attention for. The data collected will inform the development of a RPM which will be externally validated in a follow-up study.

**Discussion:** There are no RPMs that are used in clinical practice to help stratify elderly patients at high risk of MRH in the community following hospital discharge, despite this being a significant public health problem. This study plans to develop a clinically useful RPM that is better than routine clinical judgment. As this is a multi-centre study involving clinical settings that serve elderly people of heterogeneous sociodemographic background, it is anticipated that this RPM will be generalizable.

**Keywords:** Elderly, Medication-related harm, Risk prediction, Prognostic research, Public health

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## Background

Medication related harm (MRH) in older people is a significant cause of increased morbidity, hospitalisation, longer hospital stay and increased healthcare costs [1]. In people aged 65 years or older, hospital admissions attributable to medication related problems range between 5.3 to 30.7 % [1]. Adverse Drug Reactions (ADR) is a subset of medication related harm. A large prospective UK study of 18,820 patients reported a prevalence of hospital admission secondary to ADR of 6.5 %, of which almost three-quarters (72 %) were potentially avoidable [2]. Although this study considered all patients aged over 16, the average age of patients admitted with ADR was 76 years old. A more recent UK study of a hospitalized population of very elderly patients (over 80 years of age) reported an inpatient ADR incidence of 13.2 %, with 63 % considered preventable [3]. The annual cost to the NHS of admissions secondary to ADR in the UK was estimated at £466 million [2].

A study in the Netherlands of 106 medical inpatients aged 70 and over found a prevalence of severe ADR of 24 and 12 % of these elderly patients were admitted due to ADR [4].

A large, retrospective US study found that almost 100,000 elderly patients required emergency hospitalization as a direct result of ADR each year, with nearly half occurring in those over the age of 80 years [5]. A meta-analysis highlighted that the elderly were four times more likely to be admitted to hospital as a result of an ADR when compared to younger patients (16.6 % compared to 4.1 %), highlighting the increased vulnerability of an older population [6]. This increased vulnerability of the elderly population is multifactorial and includes polypharmacy, co-morbidities, renal and hepatic impairment and changes in pharmacokinetics and pharmacodynamics, cognitive impairment and altered adherence [7].

Risk prediction models (RPM) are increasingly used within healthcare to personalize and target clinical interventions. Four RPMs have been developed to date to predict ADR in older adults, although none are in current clinical use [8–11]. These models allocate scores to specific clinical parameters to identify patients at high risk of ADR during hospital admission. These four models showed at best a moderate predictive ability (Area under the receiver operator curve 0.623 to 0.73), and have not demonstrated an improvement in routine care. Three of these studies were based on prospective cohort data [9–11], whilst Onder et al's (2010) GerontoNet ADR risk score was based on retrospective data.

McElnay et al. [10] developed the first tool based on data collected from inpatients at one UK hospital. This study identified several important risk factors for adverse drug events but the model developed had low sensitivity and specificity (40.5 and 69 % respectively). Trivalle et al. [11] developed a risk prediction model based on data collected from several rehabilitation hospital units in Paris, France, that was entirely based on medications as risk variables (number of medications, use of anticoagulant, use of neuroleptic). The other two ADR risk prediction models were based on data collected from a multicentre European study (GerontoNet) and a study at one large teaching hospital in the UK (Brighton Adverse Drug Reactions Risk Model; BADRI). Both of these models (GerontoNet and BADRI) were developed to identify patients at risk of ADR whilst in hospital, and neither considered social measures as potential risk variables.

Given that at least one-fifth of hospital readmissions of elderly people in the UK are secondary to ADR [12], it is of both ethical and economic importance that elderly patients at high risk of MRH following hospital discharge are identified through objective and evidence based means. Following this process, appropriate mechanisms to reduce the risk of MRH can be initiated. The PRIME study intends to bridge this gap in prognostic research by developing a RPM to identify elderly patients at high risk of MRH at the point of hospital discharge. To our knowledge such a study has not been previously conducted. Prognostic research has thus far lacked transparency and this protocol paper is a step to addressing this issue [13]. If this RPM demonstrates a high prognostic value then it could be incorporated into local care pathways to minimize the occurrence of post-discharge MRH among elderly people. This proposal follows Medical Research Council (MRC) guidance relating to 'Developing & Evaluating Complex Interventions' which specifies the need for developmental work prior to a full evaluation [14].

### Study hypothesis

The use of a risk prediction model (RPM) to identify patients at risk of experiencing MRH will better predict these events compared to routine clinical judgment.

### Primary objective

To develop a RPM to identify elderly patients at risk of MRH in the 8 week period following hospital discharge.

### Secondary objectives

1. To compare the predictive power of the RPM to intuitive decisions (i.e. standard care) in relation to actual MRH experienced in the 8 week period following hospital discharge.
2. To determine the frequency of health care utilization secondary to MRH in the 8 week period following hospital discharge.

3. To describe the medications commonly causing MRH, the type of events occurring, their severity and preventability.
4. To describe local factors, such as ethnicity and complexity of health care systems, which impact on MRH frequency, type and severity.

## Methods/Design

The PRIME study is a prospective observational study that aims to develop a risk prediction model (RPM) that (1) can identify elderly patients at high risk of MRH upon discharge from hospital and (2) is superior to routine clinical judgment.

The PRIME study protocol was approved by the National Research Ethics Service, East of England (Norfolk; REC Reference 13/EE/0075), and was funded by the National Institute of Health Research (NIHR)- Research for Patient Benefit (RfPB) (PB-PG-0711-25094) and adopted as a Clinical Research Network portfolio study (Ageing and Primary Care).

Stage I of the study will involve a critical review of the medication RPMs in published literature, as they relate to elderly people, to inform the data collection for Stage II.

Stage II will comprise the development of a new RPM by using a prospective, observational study design to follow a cohort of 1500 elderly patients for 8 weeks after discharge from an acute care setting into the community. Patients will be invited to participate in this study during their inpatient stay and consent (or assent) obtained as close to discharge as possible. The study will collect a range of baseline clinical, medication and social data by trained research nurses that will be potential predictor variables to inform the RPM (Please see Fig. 1 and Additional file 1: Table S2). In addition, the views of the discharging medical team on the likelihood of the patient experiencing MRH will be recorded. During the 8 week follow-up MRH will be determined by a research pharmacist through patient/carer self-report via telephone interview, review of primary care records and assessment of any re-admissions to the recruiting hospital.

Along with using statistical methods to identify predictor variables from the data collected to develop the risk prediction model, an expert panel will be established to identify important predictor variables for inclusion in the model development.

### Setting

This study will be led by the Academic Department of Geriatrics (Brighton & Sussex University Hospitals NHS Trust) in collaboration with the Department of Ageing and Health (Guy's & St Thomas' NHS Foundation Trust). The study will be undertaken in acute elderly care inpatient wards at 5 NHS hospitals in the UK. Access to patient primary care information, during the 8-week follow up period, will be facilitated through the UK Primary Care Research Network.

### Population

Patients aged 65 years and over who are judged clinically fit for discharge from the acute Care of the Elderly and General Medicine wards will be eligible to participate. Written consent will be obtained from all participants. Where a patient lacks capacity to consent, their next of kin will be asked to act as a personal consultee and to support their relative taking part in the study. It is important to include those who lack capacity, as we do not wish to exclude those who are most likely to experience MRH i.e. those most vulnerable due to frailty and/or cognitive limitation. If a potential participant lacks capacity and the next of kin is not available, they will not be included in the study. Patients who consent to be included in the study will be allocated a Unique Patient Identifier Number (UPIN).

### Inclusion criteria

Patients must be over the age of 65 years at the time of recruitment and registered with a General Practitioner within the areas covered by the recruiting hospitals.

### Exclusion criteria

- Patients who lack capacity and have no nominated consultee,
- Patients that are transferred to other acute healthcare trusts (but excluding step down or intermediate care facilities),
- Patients who have a short life expectancy, due to a terminal illness

### Definitions

Medication related harm (MRH) for this study will include adverse drug reactions and a failure to receive medication, either following non-adherence or a failure in the supply chain. This definition is a modified version of the Strand (1990) definition of a drug-related problem (DRP) 'A DRP exists when a patient experiences or is likely to experience either a disease or symptom having an actual or suspected relationship with drug therapy' [15]. This definition was agreed by a panel of experts (2 Professors of geriatric medicine, UK and Netherlands; 2 consultant geriatricians, UK; Professor of clinical pharmacy and therapeutics, UK; 2 clinical pharmacists specialising in geriatrics, UK).

### Baseline data collection

Baseline data will be collected by trained research nurses including demographic (e.g. age, gender, ethnicity), clinical (e.g. discharge diagnosis, co-morbidities, renal and

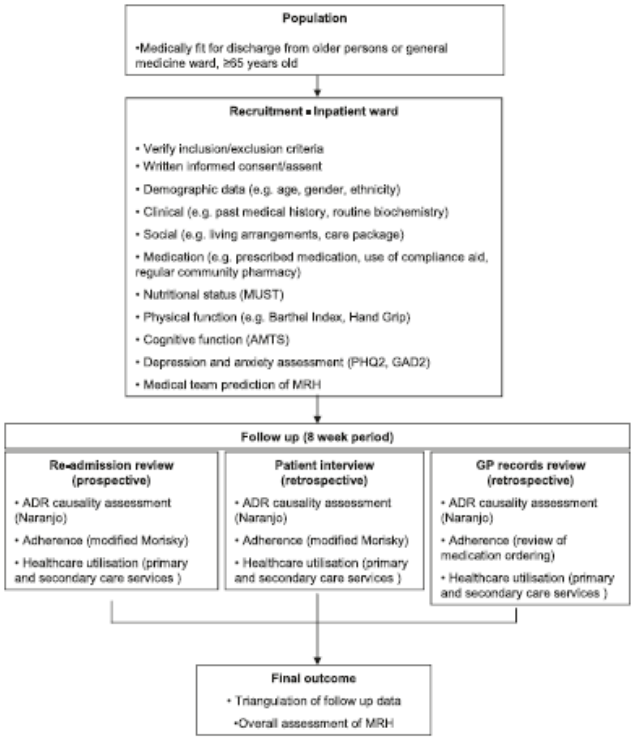


**Fig. 1** Data collection flow chart. This flow chart outlines the process that the research nurses at respective sites will use to recruit patients for the study from inpatient hosptial wards and the biopsychosocial data that was collected at baseline. The flow chart further outlines the three types of patient follow-up that will be conducted in order to determine medication harm eight weeks following hospital discharge. This includes review of any hospital re-admissions, a patient interview and review of General Practice records. These three sources of information will finally be triangulated to determine overall if medication harm has occurred

hepatic function) and social indicators (e.g. care package received and living arrangements) using a form specifically designed to allow the data to be scanned into an electronic database for future analysis. Information relating to medication name, frequency, dose and use of compliance aids will be collected and coded according to the WHO-ATC code (http://www.whocc.no/atc_ddd_index/). In addition validated tools will be used to collect information relating to nutritional status (**M**alnutrition **U**niversal **S**creening **T**ool), physical function (Barthel Activities of Daily Living Index, Hand Grip strength), cognitive function (**A**bbreviated **M**ental **T**est **S**core) and depression and anxiety (**P**atient **H**ealth **Q**uestionnaire-**2**, **G**eneralised **A**nxiety **D**isorder scale-**2**). Some of these tool are routinely measured in elderly care wards in the UK and if this was not the case the research nurse would obtain the measurement. The hand grip strength of participants will be measured using the method described in the Southampton Protocol for Adult Grip strength Measurement using the JAMAR Hydraulic Hand Dynamometer [16]. The MUST score is routinely used on elderly care wards and is a five-step screening tool to identify adults, who are malnourished, at risk of malnutrition (undernutrition) or obese [17]. The Barthel ADL Index is a validated scale used to measure performance in activities in daily living (ADL) [18].

Data will be collected directly from the hospital records, following discussion with members of the care team and with patients and/or carers.

Following discharge the junior doctor from the discharging medical team will be asked to complete a questionnaire to determine their judgement of the likelihood of the patient experiencing MRH during the 8 week follow up period. This section of the data collection form is based on the National Patient Safety Agency (NPSA) Risk Model Matrix where the likelihood of an event is rated against the consequence [19]. The junior doctor will be asked to predict the likelihood that the patient will be readmitted or access healthcare in the community due to MRH in the ensuing 8 weeks post discharge (doubtful,

possible, probable, definite) and will be asked to rate their confidence in this decision (a 6 point scale from 'little or no confidence' to 'virtually certain').

### Follow up

Eight weeks post discharge the research pharmacist at each site will conduct a telephone interview with the patient and/or carer using a standard questionnaire to determine whether the patient has experienced MRH. The patient/carer will be asked about their health service utilization over the preceding 8 weeks (GP visit, Out of Hours visit, hospital attendance/re-admission). The patient's adherence to their medications will also be determined, and the patient will be asked whether they have recognized any unwanted reactions or effects from their medications. The research pharmacists will also review the GP patient records to determine whether the patient had experienced MRH and had, as a consequence, required additional health care support.

Any re-admitted patient will continue to be followed up for the eight week period after the original discharge date and telephone follow-up and GP record data will be collected as standard.

Patients who completed their eight week follow-up period and wish to participate in the study again, following a repeat admission, will be allowed re-enter the study. They will be allocated a new UPIN which will be linked to their first UPIN to allow for sub-analysis of patients who are re-admitted to hospital.

Please see Fig. 2 for a flow-chart detailing this follow-up process.

### Decision making

- Key information required to support the research pharmacists (and consultant physicians where relevant) in determining the likelihood that the patient has experienced MRH include current medications and any recent changes to medication, assessment of patient's adherence, history of presenting complaint and ADR profile of the prescribed medicines, relevant co-morbidities, and appropriate clinical observations and investigations. MRH will be categorised as doubtful, possible, probable, or definite.
- Where an ADR is suspected the Naranjo algorithm will be utilised to support the causality assessment [20]. The Naranjo algorithm rates the causality conservatively as many of questions are not relevant e.g. did the same reaction occur when placebo was administered? Therefore it will be used as a guide to ensure temporal association, previous reports of the reaction and other possible causes are all considered when determining MRH due to an ADR.
- For an assessment of patient adherence to their medications, the Morisky scale [21] will be used.
- Where MRH is unclear, or if the admitting consultant and pharmacist cannot agree for re-admissions, cases are presented by the research pharmacist to the local End Point Committee (EPC) for further discussion and decision making.
- If a patient was re-admitted during the 8-week follow up period, data pertaining to that re-admission will be collected. The likelihood that the re-admission was due to MRH will be assessed by the research pharmacist and the admitting consultant physician using a standardized approach which incorporates the outcome from the Naranjo algorithm and the Morisky scale (as outlined above) (Table 1).

### Triangulation of outcomes

The outcomes recorded for each follow up stage (i.e. Patient telephone interview, GP records review, and re-admission where applicable) will be reviewed to determine the final outcome.

For each event the following will be recorded with the benefit of the complete follow-up by either the lead research pharmacist (JS), research fellow (NP), Professor of Clinical Pharmacy & Therapeutics (GD) or the Chief Investigator (KA):

**Table 1** The process by which Medication-related harm outcomes are recorded

| Question | Options |
|---|---|
| - 1. Do you think this patient has suffered medication related harm? | ○ Definite, Probable, Possible, Doubtful |
| - 2. How confident are you in this judgement? | ○ little or no confidence, slight to moderate confidence, <50 % confidence but a close call, >50 % confidence but a close call, strong confidence, virtually certain |
| - 3. If the patient has suffered medication related harm, what was the main cause? | ○ ADR, non-adherence, other, unable to determine |
| - What medications were implicated? | Free text entered by research pharmacist |
| - What was the clinical event of the MRH? | Free text entered by research pharmacist |
| - 4. If the patient has suffered medication related harm, was it preventable? | ○ Definitely, possibly, not preventable, not able to determine |
| 5. If the patient has suffered medication related harm, what was the severity? | ○ Fatal, life threatening, serious, significant |

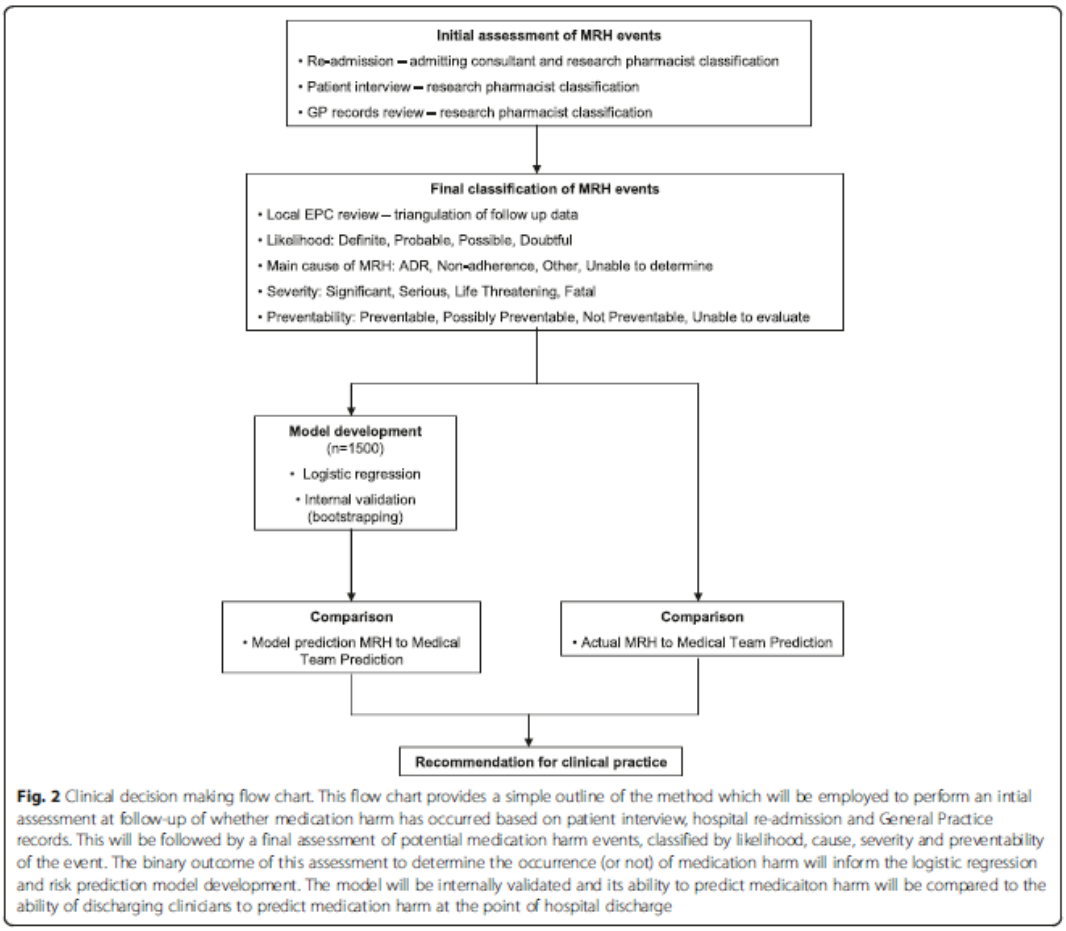


**Fig. 2** Clinical decision making flow chart. This flow chart provides a simple outline of the method which will be employed to perform an intial assessment at follow-up of whether medication harm has occurred based on patient interview, hospital re-admission and General Practice records. This will be followed by a final assessment of potential medication harm events, classified by likelihood, cause, severity and preventability of the event. The binary outcome of this assessment to determine the occurrence (or not) of medication harm will inform the logistic regression and risk prediction model development. The model will be internally validated and its ability to predict medicaiton harm will be compared to the ability of discharging clinicians to predict medication harm at the point of hospital discharge

1. Has the patient suffered an MRH? Definite; Probable; Possible; Doubtful
2. Was the MRP preventable? Definite; Possible; Not preventable
3. What was the severity? Fatal; Life threatening; Serious (hospitalisation); Serious (A&E); Serious (Community Care); Serious (Self-management); Significant
4. What was the main cause? ADR; Non-adherence; both
5. What was the event?
6. What was the drug(s)?

The total number of events and the healthcare utilization (re-admission, A&E attendance, access to out of hours services, GP or pharmacist) due to MRH will be recorded.

**Withdrawal arrangements**

Any patient who wishes to withdraw from the study is free to do so at any point without giving any reason.

**Loss to follow up**

Every effort will be made by the research pharmacist to trace participants lost to follow up. Hospital database, GP records, and contact with any named next of kin will be undertaken to determine whether the patient is still alive, their state of health at the follow up point, and if there are any new contact details.

**End of study**

The study will end when the final participant has completed the 8- weeks follow up.

### Reporting of adverse events

Adverse medication-related events will be discussed by the local EPC as appropriate and the patient's admitting physician or patient's GP will be subsequently notified.

### Sample size

The sample size calculation was determined to achieve a sensitivity of 80 % with a 95 % confidence interval width of 5 % and based on a medication related problem prevalence rate of 30 %. The nomogram designed by Carley et al. [22], based on the work of Buderer [23], was used to determine the sample size of 1500 patients. A maximum of 50 % of the total study population may be recruited from one site to reduce the risk of an unrepresentative study population.

### Statistical analysis

Data collected for the potential risk variables will undergo univariate analysis to identify the variables significantly associated with binary outcome of MRH. All variables, significant and non-significant, will be reviewed by the expert panel for clinical relevance and consistency with the literature. This will be conducted without prior knowledge of the statistical relationships of the data to avoid introducing observer bias. It is recognised that variables deemed non-significant upon univariate analysis should not be removed automatically; rather their significance should be reviewed by experts in the field, especially if the data set is small or the prevalence is rare [24]. Significant variables prevalent in less than 5 % of the study population will be reviewed and potentially rejected if they are not considered to be representative of the population. Correlation between pre-determined variables with likely interaction e.g. number of co-morbidities and number of medicines will be assessed. The dichotomisation of data, that is categorising continuous data into two groups, will be avoided where possible [25]. The variables will undergo multivariable logistic regression analysis and be eliminated or retained in the model as indicated by a combination of clinical and statistical significance.

Internal validation of the RPM using bootstrapping will follow this.

Descriptive statistics will be applied to describe population characteristics, healthcare utilisation and to identify any significant differences between those who experienced MRH and those who did not. Odds ratios will be calculated to determine the odds of a specific medication group being associated with the need for patients to access unplanned support. Multivariable regression analysis will be applied to candidate variables to identify the variables which, when combined, produce the optimal RPM sensitivity and specificity. Model calibration and discrimination will be calculated using appropriate tests e.g. Hosmer-Lemeshow and Area Under the Receiver Operating Characteristic (AUROC) curve [25]. A comparison of the predictive power of the model to the doctors' routine judgement will be conducted using appropriate statistical techniques.

## Data protection

### Participant identification, data archiving, and, storage

All patients will be given a unique study number to preserve confidentiality. This number will be entered into an appropriate database and will only be traceable to an individual patient by accessing the study form for the patient from a secure location at the Research and Development Department at each study centre. All electronic data will be password protected and only direct members of the research team will have access to the full set of electronic data generated within the study. Hard copies of all data collection forms will be stored at respective study sites for a maximum of 3 years after the study has ended.

### Ethical considerations

If during the data collection a concern is raised by the research nurse or the pharmacist, the issue will be discussed with the local Principal Investigator (PI), and advice will be given to notify the patient's GP and their clinical teams.

### Protocol compliance and deviation/violation

Notification of violation to sponsor.

## Discussion

The impact of MRH in the community, and related incidence of hospital admission has significant implications for the health and quality of life of elderly people, as well as the economic burden of avoidable primary and secondary healthcare service utilisation. Currently there is no standardized method for identifying older people at high risk of MRH upon discharge and thus there is no systematic approach to guide appropriate monitoring and intervention as needed in the community. Existing RPMs in the context of ADR in older people that have been developed for use within the hospital setting, and have shown at best a moderate performance (AUROC 0.623 to 0.73) and only two models have been externally validated [8, 9]. Therefore these prediction models are not in widespread clinical application. The aim of this study is to develop a clinically valuable and practical RPM that can identify elderly people at high risk of MRH following discharge from hospital.

It is hoped that the RPM developed through this study will alert discharging doctors of patients at high risk for whom an early medication review, follow-up and/or

adjustment of discharge medications may be indicated. A wide range of social factors (e.g. Activities of Daily Living, Accommodation status) and measurements for patient frailty (e.g. handgrip strength) are being measured in patients recruited for this study, which might support a model of higher predictive value than other tools developed in the context of MRH. Frailty has not been previously been explored as potentially important variable within a RPM for medication problems. Frailty is a common geriatric syndrome that embodies a decline in health and function associated with ageing. It is characterized by a loss of functional homeostasis such that a minor insult can result in catastrophic consequences for the individual.

A further special and key feature of this study is the comparison of the RPM that will be developed with routine risk prediction by junior doctors upon discharge of older people. This will help to determine whether the RPM developed is superior to current best practice.

It is acknowledged that asking the junior doctors to prospectively review patients' risk in this way could affect their future behavior as described by the 'Hawthorne Effect'. However, any learning effect is likely to be limited by the frequent rotation of junior doctors. Should this, however, influence the outcome of the study in such a way that raises awareness of high risk patients and results in a safer clinical judgment then this, in itself, would be a positive outcome.

### Study progress

Stage I of the study is complete, and we encourage readers to refer to the Stevenson et al. [26] systematic review of the existing RPMs to predict ADR in elderly people.

Stage II of the study is currently ongoing.

## Additional file

**Additional file 1: Table S2.** Candidate Predictor Variables. (DOCX 59 kb)

#### Abbreviations

PRIME: Prospective (P) study to develop a model to stratify the risk (RI) of medication (M) related harm in hospitalized elderly (E); MRH: Medication-related Hharm; ADR: Adverse drug reaction; RPM: Risk prediction model; EPC: End point committee.

#### Competing interests

All authors declare that they have no competing interests.

#### Authors' contributions

JS, KA, TVDC, RS, JH, GD and CR designed the study. KA, JH, GD and CR were co-applicants for the study grant. Statistical advice was provided by SB. JS, NP, KA, JT, SB, TVDC, RS, GD and CR prepared the manuscript. All authors reviewed and approved the final manuscript.

#### Acknowledgements

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#### Author details

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Received: 4 November 2015 Accepted: 6 January 2016

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# Appendix C. List of potential variables for collection

| Risk Factor | Level of importance | | | Point of collection | | | Source of data | Method of collection | Existing scale | Included in existing risk prediction tool | Include | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Essential | Desirable | Not required | Adm | D/C | Other | | | | | (✓/✖) | |
| **Medications** | | | | | | | | | | | | |
| Prescription Only Medications (POMs) | | | | | | | | | | | | |
| Over the Counter Medications (OTC) | | | | | | | | | | | | |
| When required medications (PRNs) | | | | | | | | | | | | |
| Once only medications (STAT) | | | | | | | | | | | | |
| Fluids | | | | | | | | | | | | |
| Blood products | | | | | | | | | | | | |
| Medication Name | | | | | | | | | | | | |
| Dose | | | | | | | | | | | | |
| Frequency | | | | | | | | | | | | |
| Number of doses per day | | | | | | | | | | | | |
| Route of admin | | | | | | | | | | | | |
| Duration (Acute/Chronic) | | | | | | | | | | | | |
| Change in medication | | | | | | | | | | | | |
| Medication Classification | | | | | | | | | | | | |
| Total number of medications | | | | | | | | | | | | |
| Use of compliance aid | | | | | | | | | | | | |
| Regular community pharmacist | | | | | | | | | | | | |
| Who administers meds | | | | | | | | | | | | |
| Patient/carer knowledge of the medication | | | | | | | | | | | | |
| Problems with medications - missed doses, side effects, running out | | | | | | | | | | | | |
| Patient thinks drug was responsible for admission | | | | | | | | | | | | |
| Previous ADR | | | | | | | | | | | | |

| Risk Factor | Level of importance | | | Point of collection | | | Source of data | Method of collection | Existing scale | Included in existing risk prediction tool | Include | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Essential | Desirable | Not required | Adm | D/C | Other | | | | | (✓/✖) | |
| Appropriate monitoring of medications e.g. warfarin at anticoag clinic | | | | | | | | | | | | |
| Number of prescribers (i.e. cross specialities) | | | | | | | | | | | | |
| **Social** | | | | | | | | | | | | |
| Marital status | | | | | | | | | | | | |
| Living arrangements (i.e. alone, with spouse, with family, RH, NH) | | | | | | | | | | | | |
| Smoking status | | | | | | | | | | | | |
| Alcohol consumption | | | | | | | | | | | | |
| Home nursing care | | | | | | | | | | | | |
| Monthly income | | | | | | | | | | | | |
| Volunteer work | | | | | | | | | | | | |
| Attendence at daycare centre | | | | | | | | | | | | |
| Number of times patient able to leave the house in the past 3 months as a result of their own efforts | | | | | | | | | | | | |
| Education (primary, secondary, tertiary) | | | | | | | | | | | | |
| ADL - need for assistance with one or more tasks: eating, dressing bathing transferring, toileting | | | | | | | | | | | | |
| Family support | | | | | | | | | | | | |
| Care package | | | | | | | | | | | | |
| **Biochemistry** | | | | | | | | | | | | |
| Hb | | | | | | | | | | | | |
| RBC | | | | | | | | | | | | |
| PCV | | | | | | | | | | | | |
| MCV | | | | | | | | | | | | |
| MCH | | | | | | | | | | | | |
| MCHC | | | | | | | | | | | | |
| RDW | | | | | | | | | | | | |

| Risk Factor | Level of importance | | | Point of collection | | | Source of data | Method of collection | Existing scale | Included in existing risk prediction tool | Include | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Essential | Desirable | Not required | Adm | D/C | Other | | | | | (✓/✖) | |
| WCC | | | | | | | | | | | | |
| Neutrophils | | | | | | | | | | | | |
| Lymphocytes | | | | | | | | | | | | |
| Monocytes | | | | | | | | | | | | |
| Eosinophils | | | | | | | | | | | | |
| Basophils | | | | | | | | | | | | |
| Platelets | | | | | | | | | | | | |
| MPV | | | | | | | | | | | | |
| Troponin | | | | | | | | | | | | |
| CRP | | | | | | | | | | | | |
| Creatinine | | | | | | | | | | | | |
| Urea | | | | | | | | | | | | |
| Potassium | | | | | | | | | | | | |
| Sodium | | | | | | | | | | | | |
| eGFR | | | | | | | | | | | | |
| ALT | | | | | | | | | | | | |
| AST | | | | | | | | | | | | |
| ALP | | | | | | | | | | | | |
| TBIL | | | | | | | | | | | | |
| GGT | | | | | | | | | | | | |
| Albumin | | | | | | | | | | | | |
| INR | | | | | | | | | | | | |
| APTT | | | | | | | | | | | | |
| Vit B12 | | | | | | | | | | | | |
| Folate | | | | | | | | | | | | |
| Iron | | | | | | | | | | | | |
| TC | | | | | | | | | | | | |

| Risk Factor | Level of importance | | | Point of collection | | | Source of data | Method of collection | Existing scale | Included in existing risk prediction tool | Include | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Essential | Desirable | Not required | Adm | D/C | Other | | | | | (✓/✖) | |
| LDL | | | | | | | | | | | | |
| HDL | | | | | | | | | | | | |
| Blood glucose | | | | | | | | | | | | |
| HbA1C | | | | | | | | | | | | |
| Measured serum drug concentration | | | | | | | | | | | | |
| **Medical** | | | | | | | | | | | | |
| Presenting complaint | | | | | | | | | | | | |
| Diagnosis on admission | | | | | | | | | | | | |
| Diagnosis on discharge | | | | | | | | | | | | |
| Cause of hospitalisation (ADE v non-ADE) | | | | | | | | | | | | |
| Number of acute medical problems | | | | | | | | | | | | |
| Number of past medical problems | | | | | | | | | | | | |
| Co-morbidities | | | | | | | | | | | | |
| Number of co-morbidities | | | | | | | | | | | | |
| Number of hospital admissions in past 12 months | | | | | | | | | | | | |
| Number of different visits to clinic in past 12 months | | | | | | | | | | | | |
| Number of different visits to hospital (outpatients) in last 12 months | | | | | | | | | | | | |
| Last doctor attended (GP or hospital doctor) | | | | | | | | | | | | |
| Number of visits to GP in past year | | | | | | | | | | | | |
| Length of hospital stay | | | | | | | | | | | | |
| Self-reported health over last year | | | | | | | | | | | | |
| Weight/height ratio | | | | | | | | | | | | |
| Nutrition | | | | | | | | | | | | |
| Method of feeding | | | | | | | | | | | | |

| Risk Factor | Level of importance | | | Point of collection | | | Source of data | Method of collection | Existing scale | Included in existing risk prediction tool | Include | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Essential | Desirable | Not required | Adm | D/C | Other | | | | | (✓/✖) | |
| Recent nausea/vomiting/diarrhoea | | | | | | | | | | | | |
| Temperature | | | | | | | | | | | | |
| Pulse | | | | | | | | | | | | |
| Blood pressure | | | | | | | | | | | | |
| Hearing eyesight | | | | | | | | | | | | |
| Mental/cognitive status | | | | | | | | | | | | |
| Renal failure | | | | | | | | | | | | |
| Indicators of physical function | | | | | | | | | | | | |
| Falls | | | | | | | | | | | | |
| Ischaemic heart disease | | | | | | | | | | | | |
| Diabetes | | | | | | | | | | | | |
| Infections | | | | | | | | | | | | |
| Acute stroke | | | | | | | | | | | | |
| Liver disease | | | | | | | | | | | | |
| Congestive cardiac failure | | | | | | | | | | | | |
| Angina | | | | | | | | | | | | |
| COPD | | | | | | | | | | | | |
| Hyperlipidaemia | | | | | | | | | | | | |
| **Other** | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

# Appendix D. Research Ethics Committee approval letter

**NRES Committee East of England - Norfolk**
Nottingham REC Centre
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839436

21 May 2013

Dr Khalid Ali
Senior lecturer in Geriatrics and cosnultant geriatrician
Brighton and Sussex Medical School
Academic Department of Geriatrics, Audrey Emerton Building
Eastern Road
Brighton
BN2 5BE

Dear Dr Ali

**Study title:** **Developing a tool to stratify the risk of medication harm in the elderly**
**REC reference:** **13/EE/0075**
**Protocol number:** **N/A**
**IRAS project ID:** **114225**

Thank you for your letter of 20th May 2013. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 18 March 2013

**Documents received**

The documents received were as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Interview Schedules/Topic Guides | BSUH - v1 | 13 May 2013 |
| Interview Schedules/Topic Guides | GSTT - v1 | 13 May 2013 |
| Other: GP Survey BSUH | 2 | 13 May 2013 |
| Other: GP Survey GSTT | 2 | 13 May 2013 |
| Other: Coded Data Collection Form | | |
| Participant Consent Form: BSUH | 2 | 13 May 2013 |
| Participant Consent Form: GSTT | 2 | 13 May 2013 |
| Participant Consent Form: Consultee Consent Form - GSTT | 2 | 13 May 2013 |
| Participant Consent Form: Consultee Consent Form - BSUH | 2 | 13 May 2013 |

**Approved documents**

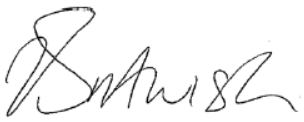
The final list of approved documentation for the study is therefore as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Covering Letter | Letter from Dr Khalid Ali | 04 February 2013 |
| Interview Schedules/Topic Guides | BSUH - v1 | 13 May 2013 |
| Interview Schedules/Topic Guides | GSTT - v1 | 13 May 2013 |
| Investigator CV | Khalid Mustafa Ali | 08 February 2012 |
| Other: GP Survey BSUH | 2 | 13 May 2013 |
| Other: GP Survey GSTT | 2 | 13 May 2013 |
| Other: Coded Data Collection Form | | |
| Participant Consent Form: BSUH | 2 | 13 May 2013 |
| Participant Consent Form: GSTT | 2 | 13 May 2013 |
| Participant Consent Form: Consultee Consent Form - GSTT | 2 | 13 May 2013 |
| Participant Consent Form: Consultee Consent Form - BSUH | 2 | 13 May 2013 |
| Participant Information Sheet: BSUH | 1 | 23 January 2013 |
| Participant Information Sheet: GSTT | 1 | 23 January 2013 |
| Participant Information Sheet: Consultee IS BSUH | 1 | 23 January 2013 |
| Participant Information Sheet: Consultee IS GSTT | 1 | 23 January 2013 |
| Protocol | 1 | 23 January 2013 |
| REC application | 114225/409838/1/67 | 25 January 2013 |

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

| **13/EE/0075** | **Please quote this number on all correspondence** |
|---|---|

Yours sincerely



**Miss Zoe Birtwistle**
**Assistant Committee Co-ordinator**

E-mail: NRESCommittee.EastofEngland-Norfolk@nhs.net

*Copy to:* *Mr Scott Harfield,*
*Scott Harfield, Brighton and Sussex Medical School*

# Appendix E. Patient information sheet

Version 2
07/10/2013

Guy's and St Thomas' NHS
NHS Foundation Trust

Department of Ageing and Health
9th Floor North Wing, St. Thomas' Hospital
Guy's and St. Thomas' NHS Foundation Trust
Westminster Bridge Road
London. SE1 7EH
Tel: 020 7188 2088

**Patient Information Sheet**

**Principal Investigator:** Dr. Rebekah Schiff
**Location/Study Site:** St. Thomas' Hospital, London

**Study Name:** Developing a tool to stratify the risk of medication harm in the elderly

---

You are being invited to take part in a research study looking at the problems elderly people can experience with their medicines e.g. taking the wrong amount of medication at the wrong time. Your participation is entirely voluntary. Before you decide whether to take part or not, it is important that you understand why the research is being done and what you are being asked to do. Please read the following information carefully. Please feel free to talk to others about the study if you wish and take your time to decide if you would like to take part.

If you are unable to read or sign this form due to your medical condition, your legally authorised representative can help you decide if you should take part and can sign this form on your behalf. When you are well enough, you will also be asked to read this form and to sign if you agree to continue taking part.

---

**What is the purpose of the study?**

We know from previous studies that many people age 65 years and over may have problems with their medicines. These problems can include forgetting to take the medicines or suffering unpleasant side effects that may result in a GP visit or hospital admission.

Our study will look at which factors are the most important in causing problems related to medications. Identifying these factors can then help us put systems in place to try and reduce problems related to medications.

**Why have I been invited?**

All patients who have been admitted to add local hospital are over 65 years old, and are registered with a GP in add local area have been invited to take part.

**Do I have to take part?**

Taking part is entirely voluntary. If you decide to take part, you will be given this information sheet and asked to sign a consent form. If you decide not to take part in the study, a member of the research team will ask you some questions to explore the reasons why you are not keen to participate. In all circumstances you are still free to withdraw at any time and without giving a reason, and your care will not be affected.

**What will happen to me if I take part?**

We will use information from your hospital notes to review the factors that may increase your risk of having problems with your medicines. The information collected from a group of patients will be used to help predict which patients are more likely to have a problem with their medications.

Eight weeks after hospital discharge, a member of the research team will phone you to ask questions about your medicines. The research team will also access your GP, and hospital records to collect information about your health and medications for 12 months after hospital discharge.

**What will I have to do?**

If you consent to take part in the study, you will not have to do anything whilst in hospital. Eight weeks after discharge, a researcher will phone and ask about your general health and medications. This phone conversation will take approximately 20 minutes. If you have difficulties using a telephone your carer may help.

**What are the possible advantages and disadvantages of taking part?**

There will be no immediate benefits, but the information we obtain from this study may help reduce the problems people have with their medicines in the future.

You will not be disadvantaged by taking part in this study as your treatment and care will not be affected in any way. You may find it inconvenient having a researcher asking you questions over the phone.

**What happens when the research study stops?**

When the study stops, your information will be kept securely and anonymously for up to 3 years and then it will be destroyed. We hope to publish the outcome of the study in a scientific journal. If you wish to have a copy of the published study, we can send this to you.

**What if there is a problem?**

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed.

If you have any concerns about your treatment or medication please contact your GP, community pharmacist or PALS (Patient Advice and Liaison Service) Tel. 020 7188 8801.

**Will my taking part in the study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential.

**Who is organising and funding the research?**

This study is a research project sponsored by the Clinical Investigation Unit, Brighton and Sussex University Hospital Trust and being conducted in various hospitals within UK. The Chief Investigator is Dr.Khalid Ali.

The research is being funded by Research for patient benefit scheme (National Institute for Health Research) and the Guy's and St. Thomas' Charity.

**Who has reviewed this study?**

This study has been reviewed, and approved, by add local R&D Research and Development Team and, NRES Committee East of England-Norfolk.

**Contact details**

Your study doctor, Dr. Rebekah Schiff (020 7188 2088), or Trial Fellow, Jennifer Stevenson (07715 802 446), will answer any questions you may have.

**Thank you for taking part in this study.**

# Appendix F. Consultee information sheet

Version 2
07/10/2013/

Guy's and St Thomas' NHS
NHS Foundation Trust

Department of Ageing and Health
9th Floor North Wing, St. Thomas' Hospital
Guy's and St. Thomas' NHS Foundation Trust
Westminster Bridge Road
London. SE1 7EH
Tel: 020 7188 2088

**Consultee Information Sheet**

**Principal Investigator:** Dr. Rebekah Schiff
**Location/Study Site:** St. Thomas' Hospital, London

**Study Name:** Developing a tool to stratify the risk of medication harm in the elderly

---

Your relative/friend is being invited to take part in a research study looking at the problems elderly people can experience with their medicines e.g. taking the wrong amount of medication at the wrong time. We feel that he/she is unable to decide for him/herself whether to participate in this research study. As you are their next of kin (Consultee) we would like to ask your opinion on the following document to see if you think your relative/friend would consent to entering into the study if they were able to make the decision. We ask you to set aside your own views and consider your relative/friend's interests and what you feel would be their wishes, and any advance decisions they may have made that you are aware of should take precedence.

Their participation is entirely voluntary. To help decide whether they would like to take part or not, it is important that you understand why the research is being done and what it will involve. Please read the following information carefully. Please feel free to talk to others about the study and take time to decide whether you wish your relative/friend to take part or not.

---

**What is the purpose of the study?**

We know from previous studies that many people age 65 years and over have problems with their medicines. These problems can include forgetting to take the medicines or suffering unpleasant side effects that may result in a GP visit or hospital admission.

Our study will look at which factors are the most important in causing problems related to medications. Identifying these factors can then help us put systems in place to try and reduce problems related to medications.

**Why has my relative/friend been invited?**

Your relative/friend has been invited to take part because they have been admitted to add name of hospital are over 65 years old and their GP is in add local area

**Do I have to let my relative/friend take part?**

Taking part is entirely voluntary. If you do decide to let your relative/friend take part, you will be given this information sheet and asked to sign a consent form on their behalf. If you decide not to let your relative/friend take part in the study, a member of the research team will ask you some questions to explore the reasons why you are not keen for them to participate. In all circumstances you are still free to withdraw your friend/relative at any time and without giving a reason, and their care will not be affected.

**What will happen to my relative/friend if they take part?**

We will use information from their hospital notes to review the factors that may increase their risk of having problems with their medicines. The information collected from a group of patients will be used to help predict which patients are more likely to have a problem with their medications.

Eight weeks after hospital discharge, a member of the research team will phone you to ask questions about your friend/relatives medicines. The research team will also access their GP, and hospital records to collect information about their health and medications for 12 months after hospital discharge.

**What does my relative/friend have to do? (What will I have to do?)**

Your friend/relative will not have to do anything. If you consent to them taking part in the study, you will not have to do anything whilst they are in hospital. Eight weeks after discharge, a researcher will phone and ask about your friend/relatives general health and medications. This phone conversation will take approximately 20 minutes. If you have difficulties using a telephone please tell the researcher.

**What are the possible advantages and disadvantages of taking part?**

There will be no immediate benefits, but the information we obtain from this study may help reduce the problems people have with their medicines in the future.

Your friend/relative will not be disadvantaged by taking part in this study as your treatment and care will not be affected in any way. You may find it inconvenient having a researcher asking you questions over the phone.

**What happens when the research study stops?**

When the study stops, your information will be kept securely and anonymously for up to 3 years and then it will be destroyed. We hope to publish the outcome of the study in a scientific journal. If you wish to have a copy of the published study, we can send this to you.

**What if there is a problem?**

Any complaint about the way you or your relative/friend has been dealt with during the study or any possible harm suffered will be addressed.

If you have any concerns about your treatment or medication please contact your GP, community pharmacist or PALS (Patient Advice & Liaison Service) Tel. 020 7188 8801.

**Will my relative/friend taking part in the study be kept confidential?**

Yes. All the information about your relative/friend's participation in this study will be kept confidential.

**Who is organising and funding the research?**

This study is a research project sponsored by the Clinical Investigation Unit, Brighton and Sussex University Hospital Trust and being conducted in various hospitals within UK. The Chief Investigator is Dr.Khalid Ali.

The research is being funded by Research for patient benefit scheme (National Institute for Health Research) and the Guy's and St. Thomas' Charity.

**Who has reviewed this study?**

This study has been reviewed, and approved, by Add local R&D and Development Team and NRES Committee East of England-Norfolk.

**Contact details**

The study doctor, Dr. Rebekah Schiff (020 7188 2088) or Trial Fellow, Jennifer Stevenson (07715 802 446) will answer any questions you may have.

**Thank you for taking part in this study.**

# Appendix G. Patient consent form

Guy's and St Thomas' NHS
NHS Foundation Trust

Department of Ageing and Health
9th Floor North Wing, St. Thomas' Hospital
Guy's and St. Thomas' NHS Foundation Trust
Westminster Bridge Road
London. SE1 7EH
Tel: 020 7188 2088

UPIN: _____

PATIENT CONSENT FORM

Title of Project: **Developing a tool to stratify the risk of medication harm in the elderly.**

Principle Investigator: Dr. Rebekah Schiff

Please write your initials in each box if you agree to each statement:

1. I confirm that I have read and understand the information sheet (version 2 dated 07 October 2013) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during this study may be looked at by individuals from the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in the study. ☐
5. I agree to my GP records being reviewed by the research team. ☐
6. I agree to take part in the above study. ☐

_____ _____ _____

Name of Patient Date Signature

_____ _____ _____

Name of Person taking consent Date Signature

Version 3
07/10/2013

# Appendix H. Consultee consent form

Guy's and St Thomas' NHS
NHS Foundation Trust

Department of Ageing and Health
9th Floor North Wing, St. Thomas' Hospital
Guy's and St. Thomas' NHS Foundation Trust
Westminster Bridge Road
London. SE1 7EH
Tel: 020 7188 2088

UPIN: _____

CONSULTEE CONSENT FORM

Title of Project: **Developing a tool to stratify the risk of medication harm in the elderly.**

Principle Investigator: Dr. Rebekah Schiff

Please write your initials in each box if you agree to each statement:

1. I confirm that I have read and understand the information sheet (version 2, dated 7th October 2013 ) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my relative/friend's participation is voluntary and that I am free to withdraw them at any time without giving any reason, without my relative/friend's medical care or legal rights being affected. ☐
3. I understand that relevant sections of my relative/friend's medical notes and data collected during this study may be looked at by individuals of the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to my relative/friend's records. ☐
4. I agree to my relative/friend's GP being informed of their participation in the study. ☐
5. I agree to my relative/friend's GP records being reviewed by the research team. ☐
6. I agree to my relative/friend taking part in the above study. ☐

| _____ | _____ | _____ |
|---|---|---|
| Name of Consultee | Date | Signature |
| _____ | _____ | _____ |
| Name of Person taking consent | Date | Signature |

Version 3 07/10/2013)

# Appendix I. Data collection frequently asked questions



## Main CRF

***Completing the CRF***

1. *Can I write multiple co-morbidities in a textbox?*

Yes. Multiple co-morbidities can be written in text boxes. However, where possible please use the tick box options available e.g. p 3 and write only one co-morbidity per box. This rule applies to symptoms and drugs also. This will assist with the analysis of the data.

2. Can I write outside of the designated box on the CRF?

Yes. Where possible this should be avoided however, data recorded outside of the designated box is usable. This may be helpful e.g. documenting additional notes that is not required for the data analysis but for the reviewer to provide a clearer clinical picture. If something is written that would like to be included in the data for analysis this should be indicated clearly e.g. circle and write "please include".

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***Bloods*** *(p7 and p19)*

3. *When collecting data on bloods (admission and discharge) how far forward or back should I go?*

Admission bloods: record up to 48hours from admission
Discharge bloods: record last value reported before discharge (if repeated since admission). Do not repeat admission bloods if bloods have not been repeated.

4. *Can I record an eGFR as >60 ml/min if this is how it is reported on the system?*

No. The software used to scan the CRFs (Formic) does not recognize < or > symbols.
Trust reporting of eGFR varies. If your trust does **not** report a specific value, e.g. 73 ml/min, when eGFR is >60ml/min then values >60ml/min should be recorded as 60 in the CRF. If your trust does report specific values, e.g. 73 ml/min, then the value should be recorded as 73 in the CRF.
Similarly, a specific value when CRP is <5 is not reported in all trusts. If your trust does **not** report a specific value, e.g. 4.2, when CRP is <5 the values <5 should be recorded as 4.9 in the CRF. If your trust does report specific values, e.g. 4.2., the value should be recorded as 4.2 in the CRF.
If you spot further anomalies similar to those outlined above please highlight to Jennifer Stevenson as these have implications for the analysis of the data.

5. *Are T4 and free thyroxine the same?*

Yes.

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***Medication*** (e.g. p6, p20-21)

6. *How do I record a reducing steroid dose?*

A reducing dose of any medication should be documented in full

7. *How do I record a short course of antibiotics?*

A short course of any medication should be documented in full

8. *My patient uses insulin, can I just write insulin?*

No. Insulin type must be recorded in full e.g. Humulin S, Humulin I or Humulin M3, Humalog Mix 50 or Humalog Mix 25, NovoMix 30. Different types of the same brand of insulin have different durations of action and are therefore used for different indications. It is not sufficient to only record e.g. Humulin.

9. *The ward pharmacist has recorded during medicines reconciliation that my patient takes paracetamol bought from the local pharmacy for occasional pain relief, should I record this as a drug on admission?*

Yes. This would be considered an Over-The-Counter (OTC) medication. If this has been documented as part of medicines reconciliation then this should be recorded e.g. Paracetamol 1g QDS PRN (OTC). There is no need to ask the patient about OTC medications.

10. *My patient is prescribed nutritional supplements on his discharge prescription, should I record this as a medication?*

Yes. All items on the discharge prescription should be recorded. If a patient is admitted taking nutritional supplements and they have been reconciled, these would be recorded in the drugs on admission section.

11. *On admission my patient was taking a short course of antibiotics which were stopped on the ward, do I record them as drugs on admission?*

Yes. If the patient was taking antibiotics for an acute infection when they presented to the hospital, these are considered to be drugs on admission. The course duration should be recorded if known.

12. *My patient has a dosette box filled by her daughter, should I record this as the patient has a dosette box?* (e.g. p5)

No. The question "Does the patient have a dosette box?" refers to dosette boxes that are filled by a **pharmacy only**. These may also be referred to as blister packs, MDS, medicines compliance aid. If the patient states that they have a dosette box, you should clarify who fills it. A more appropriate approach may be to ask "Does the pharmacy pack down your medication into a weekly box?" or "Do you receive your medications in individual packets for each medication or in a weekly box?"

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***Social data***

***Accommodation and care packages*** (e.g. p4, p12-13)

13. *Is sheltered housing the same as a warden controlled flat?*

Yes. A warden controlled flat will have a scheme manager (a warden) who lives onsite or offsite, and should provide 24-hour emergency help through an alarm system. Each scheme usually has between 20 and 40 self-contained flats or bungalows, but there will often be communal areas, such as the lounge, laundry room and garden.

14. *Is sheltered housing classified as living in an institution?*

No. Residents are independent in their self-contained flats but may have different levels of care packages to assist them with their activities of daily living. Living in an institution relates to living in a residential/care/nursing home.

15. *My patient lives in a hostel, how should I record this?*

This should be recorded as living in sheltered housing.

16. *What information should be entered into the "what care package is the patient being discharged with?" textbox?*

The care package that the patient is being discharged with should be documented in this box. This may include an existing care package (as per admission) or there may be additional care in place on discharge. For example, the patient had OD carer to help with washing and dressing in the morning but is going home with BD carers. In this instance additional care has been provided and so you would select "yes" for additional package of care. In the frequency of care box you would tick BD. In the textbox to you would describe the care e.g. twice daily carers to assist with getting up and putting to bed. If the patient was discharged with the same package of care as they were receiving prior to admission, based on the example above, you would select "no" for additional package of care, OD for frequency and in the text box write once daily carer to help with washing and dressing.

***Activities of daily living*** (e.g. p14)

17. *My patient has a stoma that is changed by her husband, how do I record bowel continence?*

There is limited information defining this area and therefore the following definitions should be applied when considering bowel continence:
- Incontinent: if unable to manage stoma independently
- Occasional accident: if requires some support with stoma
- Continent: if maintains stoma independently

18. *My patient has a long term catheter which he manages himself, how do I record bladder continence?*

Similarly to bowel continence, the following definitions should be applied:
- Incontinent: if catheterized and unable to manage
- Occasional accident: if requires some support with catheter
- Continent: if maintains catheter independently

**Junior Doctors Post-discharge Risk Rating** (p22)

**19.** What does it mean by medication related harm?

**Medication Related Harm:** "A medication related problem is an event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care"
The PRIME Study focuses on 2 potential types of harm:
**Failure to Receive Drugs:** The patient has a medical problem that is the result of his or her not receiving a drug (e.g. for pharmaceutical, psychological, sociological or economic reasons). (This includes running out of medication and problems with compliance)
**Adverse Drug Reaction (ADR):** The patient has a medical problem that is the result of an ADR or adverse effect.

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***General points***

20. *A relative has given assent for their mum to take part in the study however the patient is being discharged to a nursing home. Who's contact details should I obtain for the telephone follow up?*

The nursing home and the relative's contact details should be recorded to allow for either or both to be contacted. The pharmacist will contact the nursing home in the first instance and speak with the nurse in charge. In the event that a care homes pharmacist provides a service to the home then their knowledge may be utilized.
If the patient has capacity and has consented, where possible the pharmacist should speak with the patient directly and use

nursing home staff if needed.
**N.B.** When recruiting patients who are being discharged to a new nursing/care/residential home, confirm the location of the home and the GP providing the service. Relatives often place family members in homes which are nearer to them resulting in the GP being out of our specified area and so making the patient **not eligible to participate** in the study.

21. *Discharge data was collected for my patient but the discharge was delayed by 5 days due to a delay in setting up the package of care, do I need to re-do the discharge data for this patient?*

No. Patients should be recruited as close to the point of discharge as possible and in most cases should therefore be medically fit at the point of recruitment. In the event that a discharge is delayed due to a social problem e.g. re-instating a package of care, then the data does not need to be collected again.
In the event that a patient's discharge is delayed due to a medical issue then the data should be updated to more accurately reflect the patient at discharge. This should be done by crossing out any data which needs updating, writing the up to date data next to it, and initialling and dating the new data (as per guidelines for crossing out data in the "Completing CRF document" located in the study site file).

22. *What should I record for a patient who consented to the study but was transferred to another hospital rather than discharged?*

The patient would no longer be considered as eligible for the study and therefore no further data should be collected. Annotate on the Enrolment Log spreadsheet that the patient has been withdrawn and the reason for this.

23. Can I recruit patients who are in infected bays or isolate in side rooms?

No. Patient should not be recruited if they are in "infected bays" or side rooms where the patient has, or is being investigated for an infectious disease, e.g. norovirus/C.diff/TB.

24. Can I recruit patients whoare MRSA positive?

Yes. Patients who are MRSA positive and isolated in a side room may be recruited but appropriate infection control procedures should be adopted (refer to local trust policies).

25. Can I take verbal assent over the telephone?

No. Verbal assent cannot be taken over the phone. The NOK must be present to complete the assent form. Although the protocol does not state that we cannot do it, it equally does not specify that we can.

26. Does the month on the consent form have to be written in words?

No. Figures are acceptable for the date on the consent form.

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***Telephone follow up***

27. *I keep getting the patient's answer phone, can I leave a message?*

No. Phone messages should not be left.

28. *I called my patient one day after the 10 week window, is this ok?*

Yes. Patient should normally be followed up in the 8-10 weeks period however, slight deviation on this is permitted. Date of phone call will be collected so time to follow up can be monitored by the PRIME EPC and actions taken as required.

29. *My patient can't hear very well, is it ok to talk to a carer/relative instead?*

If a patient cannot hear very well it is ok to talk with the carer or relative, provided the patient gives permission to do so. Intelligence on the patients' ability to use the phone should ideally be captured at the point of recruitment and communicated to the Research Pharmacist via the Confidential Data Log.

30. *Since discharge my patient has been admitted to a nursing home and neither the patient nor the nurse can answer all the questions, what should I do about the missing data?*

Where patients do not want to (or relatives/nursing staff cannot) answer all the questions, leave the omitted questions blank. Triangulation of the data with the GP information and HES data should reduce the risk of missing an event.

31. *My patient attends the GP every two weeks for a routine check up, do I record each of these episodes in GP visits?*

No. Data collected in relation to healthcare utilisation during follow up is to be used to help establish if harm has occurred. Routine visits to/by e.g. anticoagulation clinics, district nurse, podiatrists, are not to be recorded.

32. *My patient was an inpatient at week 8 when I went to conduct their follow up phone call. They were home by week 9, should I still call them?*

No. This should be recorded as lost to follow up - patient in hospital. The patient should not be interviewed on the ward. The GP data collection would still take place.

33. *My patient was re-admitted, do I need to capture the details of the re-admission again during the telephone follow up?*

Yes. It is part of our method to triangulate the data in an attempt to verify the harm more robustly i.e. gather information from patient, GP and hospital to build an overall picture of the likelihood of harm. The reason for re-admission and any potential medication involvement should be explored during the telephone call.

34. *On re-admission my patient came through A&E before being admitted to a ward, should I record this as an A&E visit and a hospital re-admission?*

No. This should only be recorded as a hospital re-admission. If a patient attends A&E but is not admitted to a ward then this would be recorded as an A&E visit.

35. My patient called the ambulance but was not taken to hospital, do I record this?

Yes. This should be record in the "have you called the out of hours doctor" section.